Volume 7 **Neurology** *Number 3*

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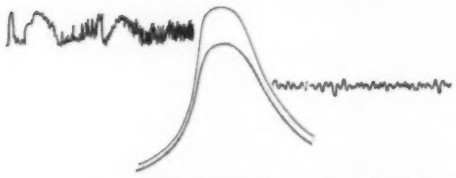

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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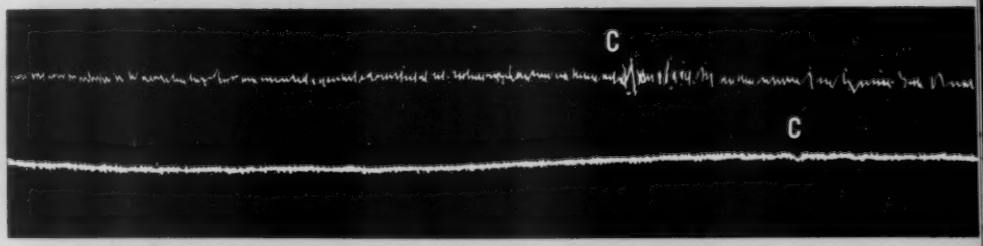

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1. Overholser, W., in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

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Volume 7 Neurology *Number 3*

Cerebral Hemispherectomy

Present Status and Clinical Indications

Robert J. Goodall, M.D.

HEMISPHERECTOMY, first described by Dandy[1] in 1928, was based upon the observation that the right frontal, temporal, and occipital lobes of the brain could be removed without producing apparent mental impairment. In his original presentation, Dandy reported five cases in which the operation was performed, all of the five patients having had a glioma. Three of the group died soon afterward, and one of the other two had not been observed sufficiently long to permit an estimate of the outcome. From the result in the remaining case, he concluded that, "Although this is scarcely an operation to be advised, it offers to those desirous of living under adverse conditions a much longer extension of life than is possible by any other form of treatment."

Thus far, more than 75 hemispherectomies have been reported. The majority were performed for tumors, chiefly gliomas, although the procedure has been applied to a number of other conditions. Gardner[2] in 1933 reported two cases in which he removed the right hemisphere for tumors. Bell and Karnosh,[3] Marshall and Walker,[4] Rowe,[5] Mensh and co-workers,[6] Zollinger,[7] and Karnosh and Gardner[8] have since employed the operation for the removal of tumors. On the whole the results have been surprisingly good, with improved mentality and personality, better muscular control, less emotional instability, more tractability, and, in some cases, a capacity to perform limited duties.

Krynauw[9] deserves credit for recognizing the value of hemispherectomy in the treatment of infantile hemiplegia. In his opinion, mental deviations and convulsive seizures are adequate indications for the procedure. He observed a material improvement in personality, mentality, and behavior postoperatively.

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Similar observations have been made by Cairns,[10] McKissock,[11] Obrador and Larramendi,[12] and Gros and Vlahovitch.[13] The author has employed hemispherectomy in the treatment of three patients, all of whom had hemiplegia, uncontrollable convulsions, evidence of homonymous hemianopsia, and severe mental changes.

From these experiences, it is apparent that hemispherectomy has a definite value in properly selected cases. As Dandy[1] pointed out, the procedure offers the most favorable prognosis when performed for tumors limited to one hemisphere. This, of course, cannot be determined definitely prior to exploration; if the evidence suggests such limitation, however, one is justified in recommending the procedure. Other indications for hemispherectomy are cerebral atrophy, porencephalic cysts, arachnoid cysts, microgyro formations, paraventricular cysts, and Sturge-Weber's disease. It is likewise promising in infantile hemiplegia associated with mental disturbances and uncontrollable convulsions and in similar disorders in adults, as well as in degenerative conditions such as unilateral hydrocephalus with unilateral cerebral atrophy, uncontrollable convulsions, mental disturbances, contralateral hemiplegia, and hemianopsia. Obviously, the more pronounced the neurologic defect, the more advantageous will be the operation.

In the future, bolder surgeons may operate for advanced hemiplegia before severe mental deterioration and convulsive seizures have developed. It may even be possible to prevent an advancing neurologic deficit if the contralateral hemisphere is capable, at an early age, of compensating for removal of the diseased hemisphere.

A complete history and thorough physical and neurologic investigation, as well as electroencephalograms, pneumoencephalograms, and arteriograms, should be a part of the examination of every patient who may be a candidate for this operation. Psychologic and visual studies may also provide valuable information, although the mental status of the patient may preclude or limit these features of the survey. Cinematography before and after surgery is useful for comparative purposes.

PROCEDURE

The majority of surgeons have employed intratracheal anesthesia and intravenous sodium Pentothal for hemispherectomy. An adequate supply of blood should be available for transfusion. Usually the operation can be performed without the induction of controlled hypotension, although this measure may serve to reduce bleeding.

Surgeons differ in their methods of removing the hemisphere. Penfield and Evans[14] pointed out that the operation should properly be called a corticectomy. McKissock[11] has emphasized the importance of removing the choroid plexus; two of his patients, in whom the plexus was left intact, developed secondary hydrocephalus necessitating subsequent surgery. Gardner[2] removed most of the caudate nucleus in a right hemispherectomy, yet ten years later Bell and Karnosh[3] reported a return of voluntary movement of the man's lower limb on the left. Cairns[10] felt that preservation of the hippocampus is important because of its connection with the hypothalamus. He also recommended preservation of the arteries to the basal ganglion from the first part of the middle cerebral artery.

Some surgeons have attempted to remove the hemisphere entirely by coagulating or clipping the veins along the longitudinal sinus and obliterating the anterior, middle, and posterior cerebral arteries. The author prefers to amputate the hemisphere by the fractional method, using an electrosurgical unit and a low cutting current. As the basal ganglia are approached, one must be extremely careful to prevent electrical damage. The use of Gelfoam will control oozing where electrocoagulation may be dangerous. After removal of the hemisphere, the dura should be tightly closed, the bone flap replaced, and the skin flap sutured in layers. Most patients readily regain consciousness after the operation.

The chief complications have been wound infection and hemorrhage. Infection usually can be prevented by the administration of antibiotics. Once it develops, smears, cultures, and sensitivity studies should be made.

If considerable bleeding is encountered at operation and oozing is suspected postoperatively, frequent dural punctures with careful attention to asepsis will probably facilitate recovery. The introduction of an infection into the dural cavity is unlikely if a rigid aseptic technic is followed.

Unless the convulsive seizures cease completely after operation, anticonvulsant medication is advisable for three to six months; thereafter, it may be withdrawn gradually.

When the patient's condition permits, the surgeon should consider it an obligation to obtain all the information possible in order to evaluate the results. Neurologic studies, as well as studies of the visual fields, roentgenograms of the skull, psychometric and psychologic tests, audiograms, and electroencephalograms should be repeated. Orthopedic measures for the correction of deformities and stabilization of joints, if indicated, should not be undertaken until after a period of one or two years.

POSTOPERATIVE RESULTS

Although the results of hemispherectomy are unpredictable, reported experiences permit a general estimate of the outcome.

Physical status. The majority of patients with hemiplegia have not exhibited any improvement in muscle strength. Preoperative and postoperative cinematography studies indicate that any improvement is due to reduction of spasticity; for the most part, spastic hemiplegia in the contralateral extremities is converted into a moderately flaccid hemiplegia. There is little danger of increasing the hemiplegia if it is well advanced, as is usually the case.

Sensory status. Sensory defects vary considerably in different patients following operation. The majority are found to have lost their finer discriminating sensations on the involved side. In most patients light touch is diminished but perceptible. Pain may be either diminished or somewhat exaggerated. Vibratory sensations are generally diminished. Heat and cold are readily distinguished; however, greater extremes may be necessary, indicating a diminution of perception. Position sense, likewise, is usually less acute, although still perceptible.

Most patients are not aware of any disturbance of olfaction, yet careful testing may show marked impairment on the side of the operation.

No extraocular muscle paralysis is to be expected. There may be slight anisocoria, although as a rule the light reflexes are normal. Fine horizontal nys-

tagmus has been observed. An homonymous hemianopsia can be demonstrated in every case. Macular sparing has also been observed and is believed to be bilateral, as stated by Walsh.[15]

For practical purposes, hearing function is not altered. Preoperative and postoperative audiograms have shown no striking differences. Penfield and Evans[14] have pointed out that some patients may actually claim better hearing on the involved side. They believe that, although hearing may be normal on the side of the operation, the ability to detect the exact source of sound may be impaired in the contralateral ear.

Usually no change in the sense of taste is noticeable postoperatively. One of Gardner's[2] patients, however, reported that taste was "thinner on the affected side."

Speech and mental status. It is generally assumed that the left hemisphere controls speech in right-handed individuals. If advanced degeneration of the hemisphere can be shown on pneumoencephalography and hemispherectomy is performed on the right in left-handed individuals, it seems unlikely that speech will be grossly disturbed. Zollinger[7] removed the left hemisphere in a right-handed patient; she was able to utter a few intelligent words postoperatively, and it was his opinion that, had she survived, her speech might have improved greatly. One of Gardner's[2] patients who was left-handed was able to speak normally following a right hemispherectomy, although his left hand was paralyzed and he was unable to write. Karnosh and Gardner[8] felt that this indicated that speech function may be situated in the intact hemisphere and right-handedness may be dictated by the opposite side.

Peripheral findings. The deep reflexes on the hemiplegic side will usually be exaggerated and the abdominal reflexes diminished. As in one of the author's patients, however, the reflexes may be essentially normal. The Hoffmann, Babinski, and confirmatory signs may or may not be present. In view of the flaccid paresis of the extremities postoperatively, pendulation with hypotonia can be expected.

Autonomic function. No pronounced changes in autonomic function following this procedure have been reported. Zollinger[15] reported extensive studies on vasomotor responses of the extremities by determination of skin temperature, but was unable to demonstrate any measurable alterations in peripheral temperature regulation on either the ipsilateral or contralateral side. In some patients intestinal motility has increased, with relief of constipation.

Electroencephalographic changes. The findings on electroencephalography have also shown considerable variation following hemispherectomy. In general, it appears that voltage is materially diminished on the side of the operation. The electroencephalogram in a case reported by Obrador and Larramendi[12] indicated that abolition of attacks of epilepsy was accompanied by slow activity in the contralateral hemisphere, which previously had been greatly disorganized. Stimulation of the side of the body on which the operation was performed produced a depression of the normal cortical rhythms. In three of their four cases Marshall and Walker[4] found that the activity on the unoperated side was markedly diminished and was unchanged on the operated side. In all four patients a rhythm in the alpha range was presented on the hemispherectomized side.

In one case photic stimulation induced a better response on the operated side, while in another case the reverse was true.

CASE REPORTS

Case 1. An 11 year old white girl had a history of a febrile illness accompanied by grand mal convulsions at the age of 11 months. Following termination of the infection, seizures persisted with a left Jacksonian component, despite anticonvulsant medication. During the previous year, the family had noticed that she seemed to be deteriorating mentally and had become extremely difficult to manage.

An electroencephalogram which had been made approximately one year previously showed a diffusely slow response with marked suppression of activity in the right occipital region, paroxysmal bursts of high voltage (2 per second) spike slow-wave complexes, which were increased by hyperventilation, and an apparently independently discharging high voltage spike focus in the right frontal region (figure 1).

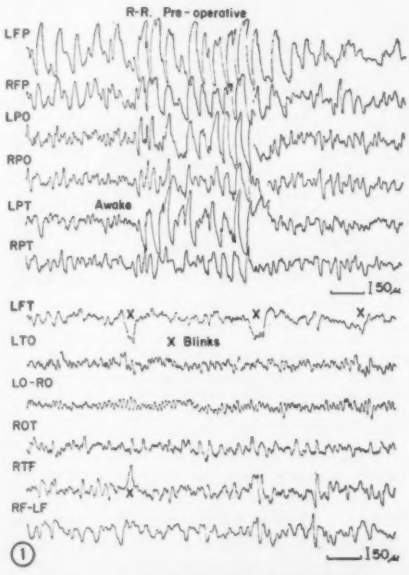


FIG. 1. *Case 1.* Preoperative electroencephalogram. Findings reported compatible with the diagnosis of a postencephalitic convulsive disorder and suggestive of both focal cortical (right frontal region) and diencephalic disease.

The child exhibited a typical left hemiplegia. The deep reflexes in both left extremities were exaggerated and a Babinski sign was present on this side. The superficial abdominal reflexes were diminished. Sensory examination revealed definite evidence of a diminution of pain and of light touch on the left. The patient walked with a spastic gait. Voluntary motion was slight in the toes of the left foot and moderate in the left ankle. Flexion and extension of the knee were fairly good. Only a minimal voluntary motion was possible in the left upper extremity; the patient could barely abduct the thumb and flex the fingers and the extremity was practically useless.

A pneumoencephalogram revealed marked dilation of the right lateral ventricle. The left ventricle appeared fairly normal, while the third ventricle was somewhat dilated and shifted slightly to the right (figure 2).

A Stanford-Binet test revealed a general intelligence of 76 per cent and a full scale intelligence quotient of 64 based upon the Wechsler-Bellevue test. According to these findings, her mental age was nine years. Visual field tests revealed a left homonymous hemianopsia with macular sparing. Visual acuity was 20/15 in each eye.

A right hemispherectomy was performed on July 24, 1953. A free bone flap was turned and the entire cortex was removed down to the basal ganglion, the hippocampal gyrus being undisturbed. The choroid plexus was left intact.

The pathologist reported that the specimen exhibited evidence of severe degenerative changes with gliosis. Several areas of marked focal atrophy were found in the frontal and occipital sections.

No anticonvulsant medication was given postoperatively, and on the twelfth day the patient had a grand mal seizure. Small doses of Dilantin and phenobarbital were instituted immediately and she had no further convulsions. Although the medication was gradually withdrawn over a period of six months, she has remained completely free of seizures to the present time, now almost three years later.

The child's mental outlook improved materially following the operation. Her aggressive,

FIG. 2. *Case 1.* Preoperative roentgenograms of skull. *A*, anteroposterior view showing hydrocephalus of entire right hemisphere, including anterior horns, body, and posterior horns. Small amount of air in anterior horn of left ventricle. No definite shift of the ventricles. *B*, right lateral brow-down view showing large hydrocephalus of the midbody, occipital, and temporal horns of right lateral ventricle. Fourth ventricle is not filled. *C*, lateral view of right ventricular septum, further demonstrating the huge unilateral hydrocephalus. Although no subarachnoid convolutional air is apparent, little cortex could remain with the large hydrocephalus.

irritable behavior ceased, she was able to get along well with her family and friends, and was a much happier, more carefree child.

Cinematography showed a marked improvement in gait and use of the left upper extremity as compared to these findings in the preoperative films, and over a period of months the patient gained further use of the arm. The previously spastic gait became more flaccid, probably accounting for the increased motor activity, since no significant improvement of muscle function could be demonstrated.

A postoperative neurologic examination revealed a left homonymous hemianopsia with macular sparing. Visual acuity was unchanged. The left corneal reflex was apparently slightly diminished. All modalities of sensation over the entire left side of the body, including the facial area, were also slightly diminished. Localization of light touch was less accurate on

the left than on the right. The deep reflexes were exaggerated. There was no Babinski sign. The abdominal reflexes were markedly diminished on the left. No cerebellar signs could be demonstrated other than those which could be explained on the basis of the paresis.

Psychometric tests were repeated at two months and again seven months following hemispherectomy. At the latter examination, the child's personality and mental efficiency appeared slightly improved, although her intellectual status was unchanged.

An electroencephalogram made two months after operation showed a remarkable change compared to the previous study. There was no evidence of activity from the right side of the head, except that which could be ascribed to reflection from the opposite hemisphere. There were occasional runs of 5 to 6 per second waves in all left leads, but no spike and spike wave complexes, as were observed in the preoperative record. Hyperventilation was not carried out satisfactorily, but showed some increase in slowing in the left hemisphere, with no abnormal forms.

In the second electroencephalogram, made approximately eight months after operation, activity of the left hemisphere was described as approaching normal (figure 3).

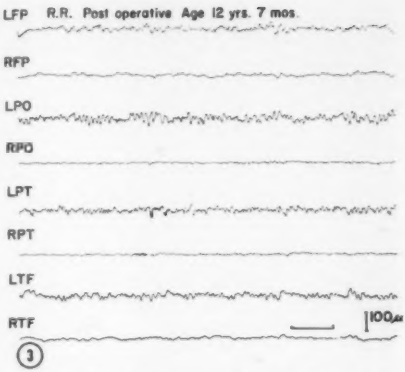


FIG. 3. *Case 1.* Electroencephalogram made eight months postoperatively. The activity of the left hemisphere approaches normal.

Case 2. A five year old white girl was examined on February 11, 1954 because of left hemiplegia and convulsive seizures. The child had a large port-wine stain on the right side of the face and anterior two-thirds of the scalp. The mother stated that she had appeared to be normal at birth, that she sat alone at four and one-half months, and walked at 22 months. She had the first convulsion at approximately four and one-half months of age during a slight febrile episode. At seven to eight months of age it was noticed that she was quite restless and that her left upper and lower extremities were weak. At the age of nine months a right parietal osteoplastic flap was turned and the family was told that a small sac of fluid was removed. Since the operation, convulsions had never been completely controlled, the paralysis of the left side had gradually increased, and the child had become extremely restless and difficult to discipline.

An electroencephalogram made in 1949 had revealed a depression of activity on the right, suggesting an extensive superficial vascular lesion of the leptomeninges. Another electroencephalogram made in October 1952 indicated extensive cortical atrophic changes in the right hemisphere, probably with an epileptogenic focus in the right frontal lobe (figure 4).

At the author's first observation, the child's hemiplegia was practically complete, although she was able to feed and to dress herself partially. She was said to have spoken a few words at the age of two years; thereafter she had become aphasic and was now able to make only a few guttural, animal-like sounds.

The patient was well nourished and, aside from the port-wine angioma over the right face and anterior two-thirds of the calvarium, her general appearance was good (figure 5). The facial muscles on the left were weak, though no extraocular paresis was apparent. A left homonymous hemianopsia was believed to be present, since she turned her head to the left in order to see objects placed directly before her. Since she could not talk, further examination of the cranial nerves was extremely difficult. The deep reflexes in both left extremities were exaggerated and Babinski and Hoffmann signs were present. The superficial abdominal reflexes were absent on the left. Pain was well perceived; the child cried out on stimulation of either side of the body and the extremities. Psychologic testing was impossible.

Plain roentgenograms of the skull revealed an extensive serpiginous type of calcification on the right side of the intracranial structure (figure 6). A pneumoencephalogram demon-

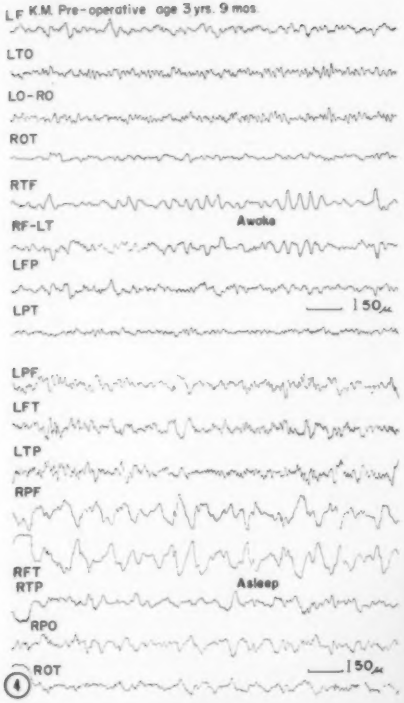


FIG. 4. *Case 2.* Electroencephalogram approximately two years prior to operation. Findings believed to indicate extensive cortical atrophic changes in right hemisphere, probably with an epileptogenic focus in right frontal lobe.

strated good filling of the subarachnoid spaces and the third, fourth, and lateral ventricles. The right lateral ventricle was slightly dilated as compared to the left; otherwise no abnormalities were observed other than the intracranial calcifications which were apparent in the plain films.

A right hemispherectomy was performed on September 16, 1954. The meninges were found to be extremely vascular, and the cortex contained numerous vascular capillary angiomatous formations throughout but most pronounced in the temporal and parietal lobes. The arachnoid was grossly thickened and almost opaque in some areas. The choroid plexus, as well as the cortex, was removed.

In order to prevent accumulation of fluid beneath the scalp flap and to keep the patient from tearing at the dressings, a plaster head cast was applied. When the cast was removed five days postoperatively, there was no fluid beneath the flap. From this experience, it appears that a cast provides an excellent means of precluding these possibilities.

The diagnosis of hemangiomatosis (Sturge-Weber's disease) was confirmed by the pathologist (figure 7).

The child was placed on a minimal dosage of anticonvulsant medication for approximately six months, and the drug was then discontinued. She has had no seizures since the operation.

Mentally this patient is much more alert, takes more notice of her environment, and is more docile and easily managed. According to the mother, she has exhibited none of her previous antisocial behavior. She is still aphasic, despite strenuous efforts to teach her to speak. Her gait has definitely improved, again probably because of an increased flaccidity of the extremities.

FIG. 5. *Case 2.* Photograph of patient showing port-wine angioma of right side of face.

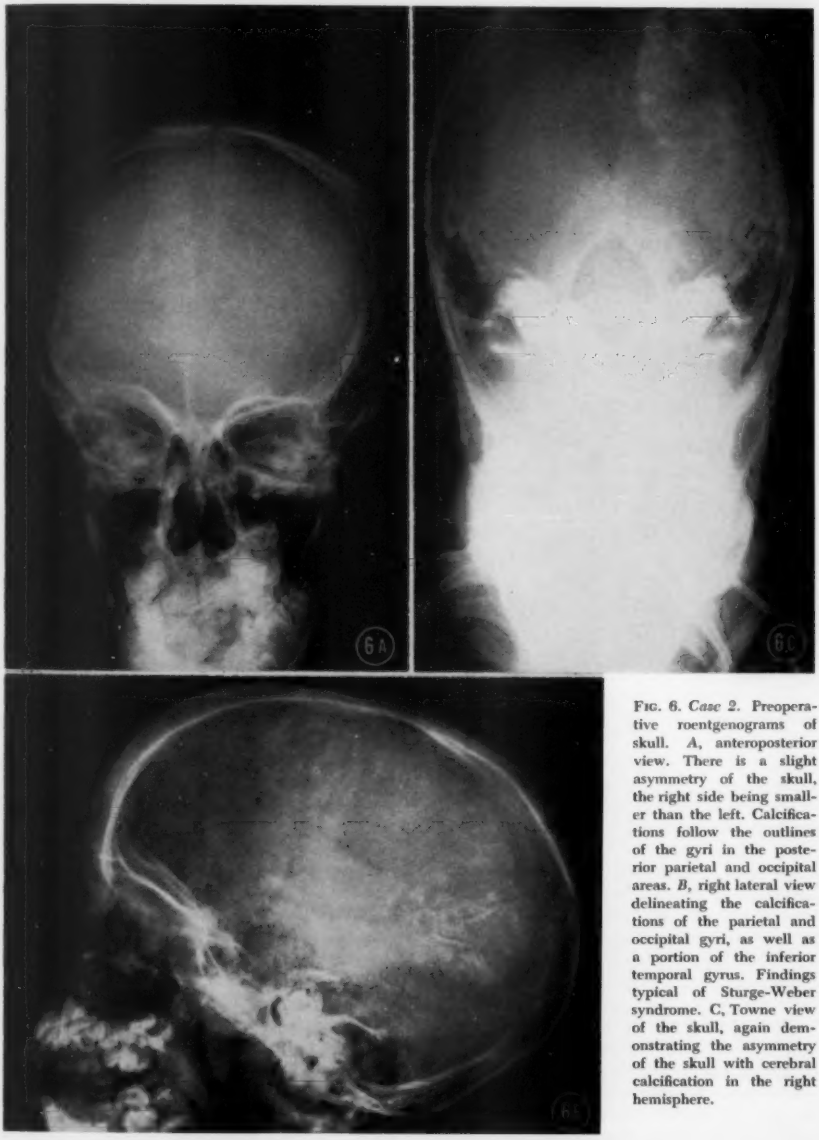


FIG. 6. *Case 2.* Preoperative roentgenograms of skull. *A*, anteroposterior view. There is a slight asymmetry of the skull, the right side being smaller than the left. Calcifications follow the outlines of the gyri in the posterior parietal and occipital areas. *B*, right lateral view delineating the calcifications of the parietal and occipital gyri, as well as a portion of the inferior temporal gyrus. Findings typical of Sturge-Weber syndrome. C, Towne view of the skull, again demonstrating the asymmetry of the skull with cerebral calcification in the right hemisphere.

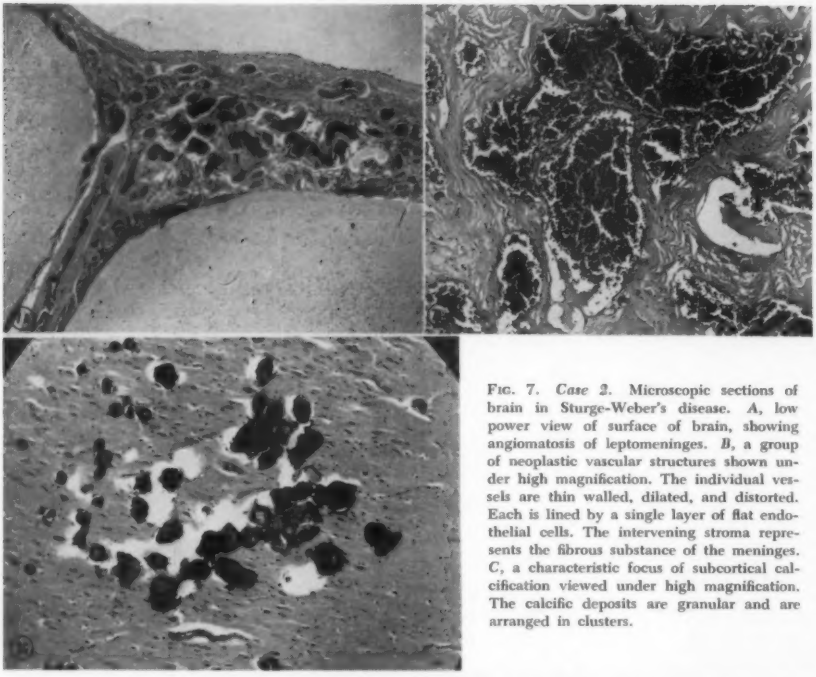


FIG. 7. *Case 2.* Microscopic sections of brain in Sturge-Weber's disease. *A*, low power view of surface of brain, showing angiomatosis of leptomeninges. *B*, a group of neoplastic vascular structures shown under high magnification. The individual vessels are thin walled, dilated, and distorted. Each is lined by a single layer of flat endothelial cells. The intervening stroma represents the fibrous substance of the meninges. *C*, a characteristic focus of subcortical calcification viewed under high magnification. The calcific deposits are granular and are arranged in clusters.

The neurologic findings were unchanged postoperatively, except for reduced spasticity of the extremities.

An electroencephalogram made approximately one month after operation showed marked changes in comparison with the study made in October 1952. There was little activity in the leads of the right hemisphere, and the activity on this side was a reflection from the left hemisphere. The activity of the left hemisphere was less disordered than in the preoperative study (figure 8). Essentially the same condition was reflected in another electroencephalogram made four months postoperatively.

Case 3. A 30 year old white woman was first brought for observation in November 1951 because of left hemiplegia and uncontrollable convulsions. According to the history, at ten months of age she had had measles accompanied by high fever, unconsciousness for several days, and convulsive movements in the left face, leg, and arm. The illness was followed by extreme left hemiplegia. By the age of 15 months she had regained use of the arm, and at two years she was walking alone. No further convulsions developed until she reached the age of nine; the grand mal seizures had continued ever since. She had been in the state hospital for epileptics for several years.

The patient was extremely difficult to examine, showing evidence of marked mental retardation. Neurologic investigation revealed no definite signs of cranial nerve disturbance other than a left internal strabismus of mild degree and a gross homonymous hemianopsia. The deep reflexes in the left upper and lower extremities were exaggerated, and the Babinski and Hoffmann signs were present. The abdominal reflexes were absent. Sensory findings were difficult to evaluate, although all modalities of sensation over the right side of the body appeared to be diminished. Motor function tests revealed a pronounced weakness of both left extremities, with typical spastic hemiplegia.

Psychometric studies indicated a mental age

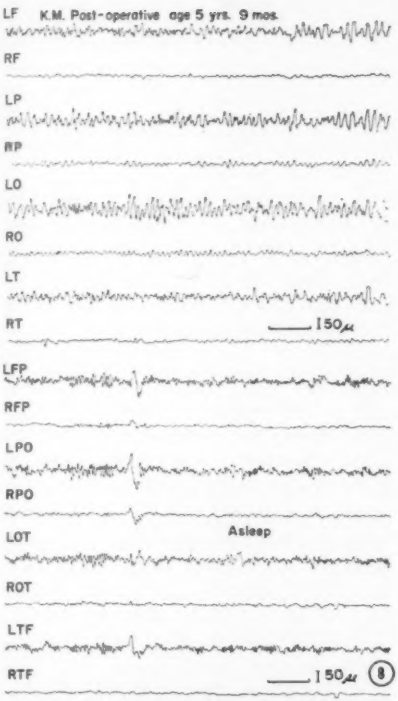


FIG. 8. *Case 2.* Posteperative electroencephalogram. There is little activity in leads of the right hemisphere and the activity on this side is a reflection from the left hemisphere. The activity of the left hemisphere is less disordered than in the preoperative study.

of approximately three years, with a general intelligence level of 20 months.

Pneumoencephalography demonstrated poor ventricular filling, and apparently a slight dilation and shift to the right of the right lateral ventricle.

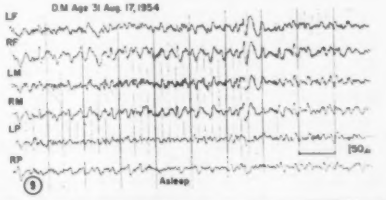
The patient was given extremely large doses of anticonvulsant drugs until August 1954. At that time she was having 20 to 30 convulsions daily, was exceedingly difficult to manage, refused to try to dress or feed herself, and frequently exhibited both fecal and urinary incontinence.

An electroencephalogram made on August 17, 1954 indicated a focus for a convulsive disorder in the anterior portion of the right hemisphere, the area covered by the frontal, motor, and anterior temporal leads (figure 9).

At operation on August 19, 1954 the entire right hemisphere was removed except for the uncus and hippocampi gyri. The choroid plexus, also, was undisturbed. The pathologist's diagnosis, following study of the specimen, was cerebral gliosis.

For several months following the operation the patient was much more alert and less belligerent, but at times she had temper tantrums and was difficult to manage. She was also able to dress and feed herself and to perform simple household tasks. Despite heavy anticonvulsant therapy, the seizures recurred three or four times every month. A neurologic examination three months postoperatively revealed essentially the same findings as before surgery, although the spasticity of the extremities and the gait had improved.

At her last observation in November 1955, one year and three months after operation, the patient was still taking moderate amounts of



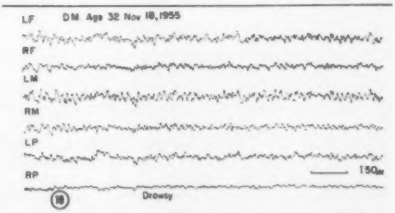


FIG. 9. *Case 3.* Preoperative electroencephalogram. The waking pattern is slow and lateralizes principal dysfunction to the right. Recurring spikes indicate a focus for a convulsive disorder in the anterior portion of the right hemisphere, the area covered by the frontal, motor, and anterior temporal leads.

FIG. 10. *Case 3.* Postoperative electroencephalogram. This is a moderately abnormal tracing. It is so classified because of the proportion of slow-wave activity in the pattern awake, and because of a tendency toward suppression of voltage over the central and posterior portions of the right hemisphere.

anticonvulsant medication, with complete control of seizures. She seemed more alert and was able to get along well with persons outside the family. As well as could be determined, there were no changes in the neurologic picture as compared to that observed at the previous examination. An electroencephalogram made on November 18, 1955 was considered moderately abnormal because of slow-wave activity in the pattern awake and suppression of voltage over the right hemisphere (figure 10). In view of the persistent seizures, anticonvulsant therapy was continued.

In this case, as was expected, the surgical results were less successful than in either of the other two. Nevertheless, the convulsions are under control and the patient is more alert and less difficult to manage.

SUMMARY

1. The literature on hemispherectomy is reviewed, with particular reference to the more significant observations.

2. Indications for the operation are discussed.

3. The importance of a careful evaluation of each patient before undertaking such a radical procedure is emphasized.

4. The findings on neurologic examination and supplementary tests are described, and the expected neurologic deficit is outlined.

5. A surgical technic is described briefly, and measures which have been found useful in preventing postoperative complications are mentioned.

6. Three cases, including the operative results, are reported.

CONCLUSION

It is generally accepted that hemispherectomy is worthwhile in selected cases. Further reports are needed to assist the neurologist and neurosurgeon in a more accurate evaluation of patients who may be candidates for the procedure.

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Carotid Angiography

A Small-Dose Technic

Capers Smith, M.D.

THE HARMFUL EFFECTS of contrast media upon the cerebral blood vessels are well known. Differences of opinion exist concerning the pathogenesis of the resultant brain damage, but there is experimental and pathologic confirmation[1–7] that the various media in current use do, under certain circumstances, alter the permeability of the cerebral vessels and produce varying degrees of arteritis or acute necrosis of vessel walls with cerebral edema and perivascular hemorrhages.

Numerous clinical studies[8–16] support the view that the severity of vascular injury and, consequently, brain damage, is directly proportional to: 1) the concentration of the solution of radiopaque contrast medium (dye); 2) the amount of dye used for each injection; 3) the total amount of dye used at one procedure; and 4) the time interval between successive injections.

A clinical study of carotid angiography was undertaken at the North Carolina Memorial Hospital with the purpose of controlling these variables without sacrificing diagnostic accuracy.

METHOD

1. Only Diodrast (35 per cent solution) was used.

2. Not more than 5 cc. was used for a single injection.

3. Not more than 30 cc. was used for unilateral study.

4. An interval of not less than ten minutes was allowed between injections.

5. An effort was made to perform the test as best suited the clinical diagnosis, rather than in a routine manner.

Since adopting this policy in December 1954, 63 angiograms have been done on 50 patients, of whom three-fourths were in the 30 to 60 age group. All studies were done by the percutaneous method. Local anesthesia with 1 per cent solution Procaine after intramuscular or rectal paraldehyde was used in all cases, except one child who was given vinyl ether anesthesia.

The use of 5 cc. injections created problems not occurring with 10 cc. volumes, but, with experience, good films in series were regularly obtained. Smaller doses than 5 cc. were inadequate for most purposes.

The essence was to maintain concentration of the dye and yet to fill those parts of the cerebral vascular tree important in the diagnosis. Therefore, success of the method depended largely upon the following: 1) rapid injection

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of the dye; 2) care to prevent dilution of dye in the syringe by blood; and 3) exposure of the films at the critical moment.

The Picker craniograph used in these studies permitted the exposure of three films following a single injection of dye. Cassettes were removed manually, and the times of initial and succeeding exposures were chosen by the operator according to the phases of the circulation most likely to be informative.

Thus, in suspected aneurysm or arteriovenous malformation, the operator made every effort to fill the arterial tree completely (figures 1 and 2). To empty a 5 cc. syringe through an 18 gauge needle, 1 second was required. Therefore, with an x-ray time of 0.5 second, the operator directed exposure of the first film as soon as 3 cc. dye had been injected, the two remaining films being exposed and removed as rapidly as possible thereafter. If arterial and venous circulations were thought to be of equal importance, the arterial was caught by exposing the first film at the end of the 5 cc. injection (figures 4 and 5). Subsequent exposures were then made after 2.5 to 4 seconds in order to show venous filling (figure 3). If the initial films were not entirely satisfactory, the reasons were obvious. If, for example, the operator had injected the dye too slowly, there was poor contrast. If a particular phase had not been shown, he corrected for this failure in the next series by allowing either longer or shorter intervals between film exposures, taking into consideration any unusually prolonged or shortened circulation time. It was thought safer to repeat, after ten minutes, a 5 cc. injection if unsatisfactory, than to give a single 10 cc. injection, even though the latter was easier, technically.

The studies reported were done by eight different operators working with combinations of ten to 12 different x-ray technicians. Some were experienced, while others were beginners.

TECHNICAL RESULTS

Of 63 angiograms, 56 were done strictly within the limits of the general policy described above, and 50 of these were of diagnostic quality. All of the six failures were attributed to faulty technic, such as external carotid artery injection, injection of dye into the neck, or poor timing.

The technic was violated in seven instances. In all of these the diagnosis had been made previously by the small-dose method, but larger doses of dye were used in the hope of getting better delineation of the lesions. In one case, that of a large arteriovenous malformation, 10 cc. of dye revealed the extent of the lesion better than 5 cc. In another, an aneurysm of the anterior cerebral artery was found to fill more completely when the larger dose was used. In the remaining five, the technical violation added no information to the diagnosis of one intracerebral clot, one arteriovenous malformation, one aneurysm, and two normal studies.

To obtain the 50 studies of diagnostic quality, the smallest amount of dye used for one complete procedure in adults was 8.0 cc.; the largest, 30.0 cc. The average total amount of dye used was 15.3 cc. It should be understood that, in addition to the usual anteroposterior and lateral projections, special views were made in one-third of the studies.

In 47 of the 50 studies, the contrast medium was injected into the common carotid artery; in only three was the internal carotid entered directly.

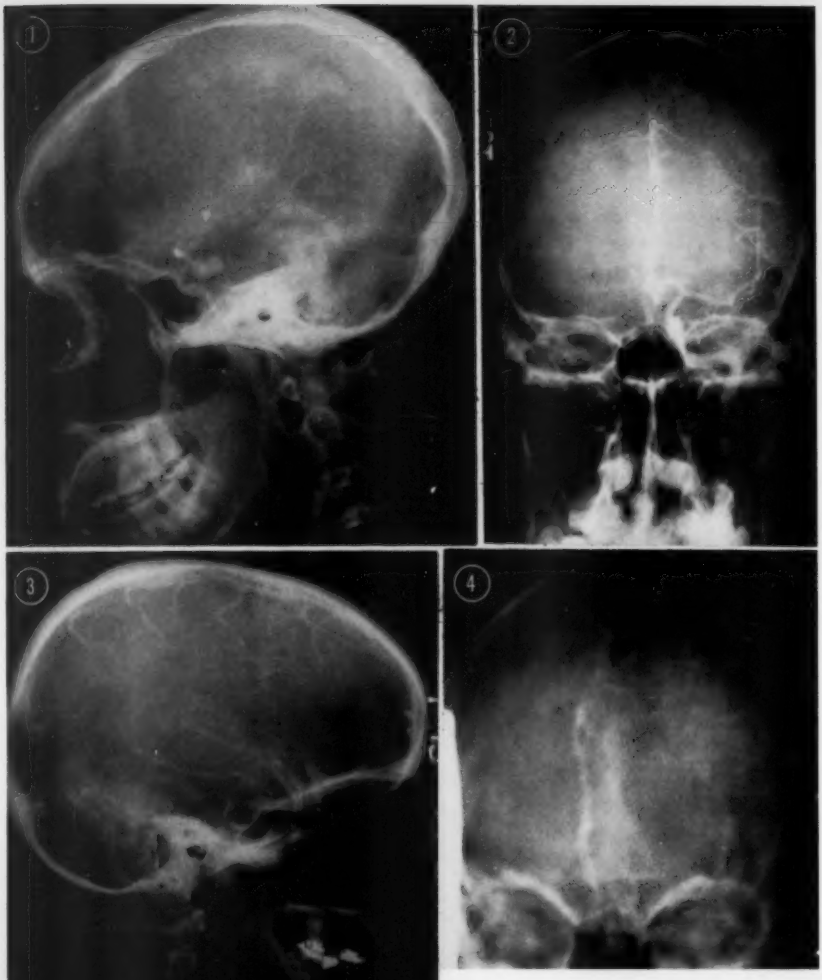

FIG. 1. Early arterial phase, lateral view, demonstrating lobulated aneurysm of right posterior communicating artery. Note dilution of dye, primarily due to slow injection. (Common carotid injection of 5.0 cc. 35 per cent Diodrast solution).

FIG. 2. Midarterial phase, anteroposterior view, demonstrating small aneurysm of anterior communicating artery (lesion was better seen in oblique views). (Common carotid injection of 5 cc. 35 per cent Diodrast solution).

FIG. 3. Midvenous phase, lateral view. Normal angiogram. Note dilution of dye. (Common carotid injection of 5 cc. 35 per cent Diodrast solution).

FIG. 4. Late arterial phase, anteroposterior view (same case as figure 3). (Common carotid injection of 5 cc. 35 per cent Diodrast solution).

FIG. 5. Late arterial phase, lateral view, demonstrating intracerebral hematoma deep in the right hemisphere. (Common carotid injection of 5 cc. 35 per cent Diodrast solution).

DIAGNOSTIC RESULTS

In the 50 patients there were 22 abnormal angiograms: seven aneurysms, two arteriovenous malformations, two intracerebral hematomas, three occlusions of the internal carotid artery, one hydrocephalus, six tumors, and one tumor suspect. There were 28 negative studies: seven subarachnoid hemorrhages, seven epilepsies of late onset, one chronic lymphatic leukemia with a frontal lobe syndrome, three suspected subdural hematomas, nine tumor suspects, and one brain abscess suspect.

COMPLICATIONS

In the entire group studied there were no significant extracerebral complications. Among the 56 angiograms done while adhering strictly to the prescribed technic, there occurred one intracerebral complication, that of a grand mal seizure in a known epileptic who had been given no anticonvulsant drugs for ten days.

Among the seven angiograms which violated the prescribed technic, there occurred one temporary hemiplegia during one of the injections and one death three and one-half days following angiography. The case histories were as follows:

Case 1. Temporary hemiplegia. A 30 year old man had a subarachnoid hemorrhage from an aneurysm of the anterior communicating artery. The aneurysm was demonstrated with the small-dose technic and without complication. Angiography was repeated one week later to obtain special views. He received two injections of 5 cc. of dye into the right common carotid artery with a ten to 15 minute interval after each. An additional 15 cc. was given within a period of five minutes, followed by another 5 cc. five minutes later. Left hemiplegia occurred immediately, but the patient had recovered completely within 12 hours. It appears that violation of the time interval rule may have been responsible for this reaction.

Case 2. Death. A 42 year old white woman was in coma, with raised blood pressure, periodic breathing, and a left hemiplegia. With the first two injections of 5 cc. of dye, a large hematoma was shown in the right cerebral hemisphere. To obtain special views one additional 5 cc. injection and three 10 cc. injections were made. Increased respiratory difficulty ensued. The patient died three and one-half days later.

The usual time interval had been allowed between injections, but the maximum single dose was doubled on three occasions and a total of 45 cc. of Diodrast was used. The woman was critically ill when the study was done, but the change in respiration immediately following the procedure suggests additional brain swelling incident to the examination. The angiographic procedure may have played a part in increasing the tentorial herniation from which she died three and one-half days after the study.

DISCUSSION

The small-dose technic has not been ideal, since more than two injections of dye were necessary in 35 of the 50 cases. However, more than three injections were required in only 17 cases. One-third of these extra doses were necessary in order to get special views; the remainder were for the most part due to improper technic: the dye had been injected too slowly, or had become too diluted with blood, or the timing had been incorrect. Because the rapid injection of dye is so important to the success of this technic, its possible hazard must be remembered. It has been stated that no appreciable rise in distal arterial pressure results from a carotid injection,[17] and it is recognized that pressures within an aneurysm do not necessarily correspond to those of the parent vessel. Nevertheless, knowledge on this matter is incomplete, and the possibility remains that rapid injection may be dangerous, particularly in aneurysms so placed as to receive the full pressure effect. Reported instances of such acci-

dents are so few in the abundant literature that rapid speed of injection has not been considered objectionable on practical grounds.

It is important to stress that, in every instance, the test was performed in the manner best suited to the clinical diagnosis. An attempt was not made to demonstrate all phases of the angiogram but, with care, any particular phase could be obtained satisfactorily.

Perhaps diagnoses have been missed that could have been made with larger volumes of dye, but there has been no reason to believe that such has happened, and the diagnostic results in this short experience compare favorably with those obtained by other workers using larger amounts of dye.[7,11,12,15] When used in this series, volumes greater than 5 cc. failed to add any significant information to that already obtained by the small-dose method.

This series is too small to permit judgment upon the added safety of the 5 cc. technic. However, the two serious complications encountered followed larger doses of dye than routine in one instance and, in the other, gross violation of the minimum time limit between injections.

SUMMARY

1. Sixty-three consecutive angiograms were done on 50 patients, using 35 per cent Diodrast solution. In 56 of these, a technic employing maximum single doses of 5 cc. and maximum total doses of 30 cc. was used; a time interval of ten to 15 minutes was allowed between injections. In seven studies this policy was violated.

2. Fifty of the 56 angiograms done with the small-dose technic were of diagnostic quality. A grand mal seizure in one patient was the only intracerebral complication.

3. The seven studies which violated the prescribed technic were of diagnostic quality; one temporary hemiplegia developed during angiography and one death occurred three and one-half days after the study.

4. The method, observations concerning the important factors in its successful use, and the results have been discussed from the standpoint of diagnostic accuracy and relative safety.

CONCLUSIONS

Although individual susceptibilities undoubtedly vary and although there is no clear evidence of a dosage threshold of toxicity, it is known that large amounts of contrast media, rapidly repeated, are more harmful to the brain than small doses given at ten to fifteen minute intervals. It is therefore reasonable to use the smallest dose compatible with efficiency, to separate the injections as widely as possible, and to accept these limitations in ease of procedure if complications are thereby reduced.

The technic employing 5 cc. doses of 35 per cent Diodrast solution, given at intervals of not less than ten minutes, has been as satisfactory as when larger quantities have been used.

My thanks are due to Dr. Thomas W. Farmer, professor of neurologic medicine, and Dr. Ernest H. Wood, professor of radiology, for their help with this work.

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■ Hippocrates knew nothing distinctly concerning the nature and uses of the nerves, though he seems to have had some confused notions respecting the nervous power, which, however, he places in the veins. If the spirit, he says, which flows through the veins be stopped or interrupted, the part in which it is stopped becomes impotent: thus, in sitting or lying down, when the veins are compressed so that the spirit does not pass through them, a torpor is immediately induced. He confounds the nerves sometimes with the veins, sometimes with the ligaments and tendons.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Increased Intracranial Pressure in Chronic Lung Disease

Charles C. Carter, M.D. and Theodore J. Fuller, M.D.

THE PURPOSE of this paper is to describe the occurrence of papilledema in emphysema in order to present an unusual, but probably not rare, cause of papilledema. Attention will be given to the possible mechanism of production of papilledema.

Deviations from the usual intravascular concentration of blood-formed elements and blood oxygen and carbon-dioxide concentrations may produce changes in the funduscopic appearance of the retina. Such changes as "cyanosis retinae,"[1] "fundus polycythemicus,"[2] and papilledema may accompany cyanotic congenital heart diseases, polycythemia rubra vera, and the polycythemia which is secondary to chronic lung diseases. Cases of papilledema in emphysema are infrequently reported in medical literature. Probably the earliest reported case was by Cameron in 1933.[3]

Interest in this subject is accentuated by recent advances in the understanding and treatment of chronic pulmonary disease and its complications. Chronic pulmonary disease is manifested by pathologic changes in the alveolar and pulmonary capillary walls which tend to produce impaired alveolar-capillary gas exchange, increase in content and partial pressure of carbon dioxide in the alveolar air, increase in free carbon dioxide and carbonic acid in arterial blood, and resultant respiratory acidosis. Respiratory acidosis may or may not result in lowered arterial pH, depending upon the ability of the body to compensate metabolically through the chemical regulation of arterial pH.[4] Chronic pulmonary disease may also be accompanied by a secondary polycythemia (erythrocytosis) as a manifestation of a physiologic response to chronic anoxia.[5]

The gross mechanisms responsible for edematous changes in the optic nerve head are increased intracranial pressure, obstruction of the venous circulation of the optic nerve head, inflammation of the tissue of the optic nerve head, and decreased intraocular pressure. Some of the physiologic and pathologic mechanisms causing "swelling and blurring" of optic disks have been fairly well worked out, but much is still speculative.[6,7] Consideration of the cause of papilledema in pulmonary emphysema must include a number of concurrent physiologic changes, any one of which may contribute to the causation of increased

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intracranial pressure. These are: 1) increased venous pressure with or without increased cerebrospinal fluid pressure, 2) secondary polycythemia (erythrocytosis), and 3) changes in carbon dioxide concentration and pH of the blood.

CASE PRESENTATION

The following case is presented as an illustration of papilledema associated with pulmonary emphysema, with subsequent alleviation after elimination of respiratory acidosis.

A white male taxicab driver, 52 years of age, was admitted to Barnes Hospital on October 27, 1954, with symptoms of chronic respiratory insufficiency of eight years' duration. Two weeks prior to admission he had been seen in the outpatient department where physical examination revealed signs of chronic obstructive pulmonary emphysema. Polycythemia was manifest by ruddy complexion, dusky mucous membranes, and engorged retinal veins. There were no retinal hemorrhages or exudates and papilledema was absent. Bronchodilators were prescribed, but symptoms progressed. One day prior to admission to the hospital continuous diffuse headache commenced and mental confusion became apparent. Past history and review of symptoms were not remarkable.

At the time of admission the temperature was 36.5° C., pulse 96 per minute, respirations 24 per minute, and blood pressure 130/80. He was very dyspneic at rest. There was intense cyanosis of the mucous membranes and nail beds. The extraocular movements and pupillary reactions were normal. Funduscopic examination revealed bilateral one to two diopter papilledema, with numerous fresh flame-shaped hemorrhages about both optic disks. The retina itself was dusky and the retinal veins engorged. The lungs were hyperresonant and the breath sounds distant to absent with a few moist inspiratory rales over the left upper lobe. The cardiac rhythm was normal sinus in character. The second pulmonic sound was accentuated. The liver and spleen were not palpable. There was no clubbing or edema. Neurologic examination was not remarkable, except for impairment of recent memory.

Laboratory data. Blood count revealed red blood cells 7.97 million, hemoglobin 21.6 grams, white blood count 6,800 with normal differential pattern, and "adequate platelets." Hematocrit was 74 per cent. Urinalysis revealed a specific gravity 1.030, pH 6.0, protein and carbohydrate negative, sediment unremarkable. Stool was guaiac negative, blood cardiolipin negative, and blood carbon dioxide combining power was 44 mEq. per liter.

Hospital course. On the day of admission, roentgenographic examination of the chest showed pulmonary congestion and minimal cardiomegaly. Electrocardiographic diagnosis indicated "marked clockwise rotation, consistent with pulmonary emphysema." Skull roentgenograms were negative. Electroencephalogram revealed "irregular slow dysrhythmia, nonfocal, consistent with organic brain changes." A lumbar puncture was then performed. Cerebrospinal fluid pressure was 400 mm. of water and the fluid was crystal clear. Because of the high pressure, no fluid was removed for cell count or protein determination. Basilic venous pressure was 132 mm. of saline and the arm-to-tongue circulation time (Decholin, normal 10 to 16 seconds) was 24 and 29 seconds on successive trials.

Pulmonary function studies revealed an estimated maximal breathing capacity of 95 liters per minute. Actual maximal breathing capacity was 58 liters per minute. Total lung volume was 6980 cc. and residual lung volume 4330 cc. Ratio of the residual lung volume to the total lung volume was 62 per cent (normal less than 35 per cent).

It was felt that the primary disorder was pulmonary emphysema. Therapy was instituted accordingly, with broad antibiotic coverage (penicillin and streptomycin) and bronchodilators (aminophyllin intravenously and rectally, ephedrine orally). An aerosol mixture of Isuprel and Alevaire was administered by manual nebulizer every two hours. On hospital days 1, 2, 3, 5, and 7, phlebotomies were performed, with resultant total removal of 2300 cc. of blood and decrease in the hematocrit to 55 per cent. During the first hospital week the patient was placed in the Drinker tank respirator eight hours daily, with continuous nasal oxygen.

By the end of one week there was evidence of improvement. Headache, mental confusion,

dyspnea at rest, and cyanosis cleared completely. The papilledema seemed stationary. The blood carbon dioxide combining power had decreased to 30 mEq. per liter. Antibiotics were withdrawn, as was the Drinker respirator. Aerosol bronchodilators were continued for the rest of the hospital stay, but were given by intermittent positive pressure in inspiration by the Bennett respirator. Blood count on the eighth hospital day revealed a red blood cell count of 6.03 million, hemoglobin 18.4 grams, white blood cell count 5,800, and platelets 2,020,000. Subsequent platelet counts were within the normal range. In view of the marked pulmonary disease, normal white blood cell level, absence of a palpable spleen, and the subsequent normal platelet counts, the hematologic diagnosis was secondary polycythemia.

At the end of the second hospital week the patient felt completely well and had resumed normal activity about the ward. A repeat electroencephalogram was reported as "much improved over previous record and now compatible with patient's age. The previously described slow activity is no longer present." Repeat lumbar puncture revealed an initial pressure of 190 mm. After removal of 3 cc. of crystal clear fluid, the closing pressure was 160 mm. No cells were seen. Protein content was 50 mg. per cent. Funduscopic examination showed beginning reabsorption of the hemorrhages and recession of the papilledema. The blood carbon dioxide combining power at the end of the second hospital week was 28.1 mEq. per liter.

After hospital discharge the patient was followed at 14-day intervals in the outpatient department of Washington University School of Medicine. On January 17, 1955, two and a half months after therapy was first instituted, no papilledema was evident. At this time blood counts were as follows: red cell count 5.48 million, hemoglobin 16.8 grams, white cell count 5,800 with normal differential. The blood carbon dioxide combining power was 33.7 mEq. per liter. The patient felt well and had returned to regular employment as a cab driver. He denied all discomfort and stated he had been active in a regular bowling league without recurrence of symptoms.

During the preparation of this report, the patient suddenly expired in his cab at work. He had been free of symptoms prior to his death.

COMMENT

The fact that an increase in cerebrospinal fluid pressure will result from an increase in the venous pressure of the jugular veins is well known and forms the basis for the Queckenstedt, Tobey-Ayer, and Grant-Cone tests. It seems doubtful that increased intracranial venous pressure arising from extracranial venous obstruction can produce papilledema. High venous pressures are frequently noted in patients with right heart failure. Superior vena cava obstruction syndromes produce an increase in jugular venous pressure. Bilateral jugular vein ligation is often performed during neck dissection surgery for the removal of malignant tissue.[8] Papilledema is not a part of these syndromes. Even complete obstruction of one or more dural sinuses may not result in papilledema or increased cerebrospinal fluid pressure. Bedford,[9] as a result of experiments on dogs, concluded, "1) the rise of cerebrospinal fluid pressure which follows obstruction of the external jugular veins or of the lateral sinuses is a temporary phenomenon, and 2) an abnormally high torcular venous pressure is compatible with a normal cerebrospinal fluid pressure."

Increase in concentration of formed elements in the blood stream may change the dynamics of intracranial venous pressure. Loman and Dameshek[10] discussed this problem after recording the case of a patient with secondary polycythemia of probable pulmonary origin with papilledema, increased cerebrospinal fluid pressure, a basilic venous pressure of 8 cm. of water, and internal jugular pressure of 30 cm. of water. No carbon dioxide combining power was reported. They postulated "thickening of the blood, relative venous stasis or slowing

and damming of venous blood in the rigidly enclosed sinus and cerebral veins" as the source of the increased intracranial pressure leading to papilledema.

This description coincides well with what seems to occur in the retinal blood vessels in patients with cyanotic types of congenital heart disease or secondary polycythemia described in ophthalmologic literature as "cyanosis retinae." Kronfeld defined the retinal picture as "characterized by very pronounced widening and tortuosity of all the visible blood vessels and a very dark, bluish-purple color of the blood within the vessels." He implicated "slight diffuse cerebral edema, enormous dilatation of intracerebral blood vessels and large central vessels within the optic nerve crowding nerve fibers within the pial coat" as possible factors in producing the papilledema.[1]

Nevertheless it is unlikely that polycythemia is the main factor in the production of papilledema. The disease polycythemia rubra vera combines the presence of increased total blood volume and increased red and white cell volume, yet papilledema is infrequently seen.[11] In a series of 163 cases of polycythemia vera, four cases of papilledema were noted by Tinney, Hall, and Giffin.[12]

Simpson[13] in 1948 seems to have been the first author to consider the role of changes in blood carbon dioxide concentration in the production of the papilledema seen with emphysema. He presented three cases and demonstrated increased cerebrospinal fluid pressure in the two who had lumbar punctures. He also presented evidence to the effect that increased venous pressure probably is not of vital importance. He gave 7 per cent carbon dioxide and 93 per cent oxygen through an oronasal type BLB mask to six patients not suffering from intracranial or vascular disease, while recording the cerebrospinal fluid pressure. In each case relevant rise in cerebrospinal fluid pressure was obtained. He suggested in his summary that, "O_2 lack and CO_2 accumulation in the arterial blood in emphysema may produce cerebral vasodilatation adequate to raise the cerebrospinal fluid pressure to above the level producing papilledema."[13]

Earlier authors have documented the effect of increased blood carbon dioxide on the caliber of pial vessels and the rate of cerebrospinal fluid secretion experimentally in animals.[14–15] More recently, the use of the nitrous oxide method of cerebral blood flow determination has demonstrated that increases in blood carbon dioxide concentration produce increase in cerebral blood flow in man.[16] This effect is felt to be secondary to cerebral vasodilatation. Further evidence for the production of increased intracranial pressure by increased blood carbon dioxide is noted by the increased cerebrospinal fluid pressure produced by inhalation of high concentration of carbon dioxide and accumulation of endogenous carbon dioxide in diffusion respiration in dogs.[17] The role of acid pH changes in the production of cerebrovascular dilatation is not as definite as that of carbon dioxide.[18]

Increased blood carbon dioxide is probably more important in the production of increased intracranial pressure in papilledema in patients with chronic pulmonary disease than are polycythemia and increased venous pressure. The fact that treatment is directed toward the alleviation of all three of these forms of disturbed physiology makes the comparative evaluation of their individual

importance difficult. In the case presented here, the decrease in cerebrospinal fluid pressure, decrease in papilledema, and improved sensorium coincided well with the return of blood carbon dioxide to normal values. It must also be recognized that phlebotomy decreased the concentration of blood formed elements which also returned toward a normal value as improvement occurred. One must conclude that increased carbon dioxide, polycythemia, and increased venous pressure must be evaluated individually in each case of chronic lung disease with central nervous system symptoms, and therapy should be so directed as to bring about return to the normal physiologic values of each.

Stone and co-workers[19] pointed out the part played by pulmonary infection in the precipitation of "decompensated respiratory acidosis." They recommended the use of antibiotics, expectorants, and bronchodilators to eliminate or prevent infection in the alveoli, liquefy alveolar secretion, and promote free expectoration. Judicial use of phlebotomy helps in decreasing the concentration of blood-formed elements and should be used at intervals until the hematocrit reaches a level of 50 to 55 per cent.

Recently the subject of the effect of chronically increased blood carbon dioxide concentration on the respiratory regulation center has come under consideration. It is postulated that chronic increases in blood carbon dioxide concentration decrease or eliminate the sensitivity of that part of the central nervous system responsible for respiratory regulation by changes in blood carbon dioxide. This leaves the chemoreceptors in the carotid arteries as the prime respiratory regulators, necessitating a decrease in blood oxygen concentration for the production of respiratory stimulation. The dangers of producing an increase in blood oxygen concentration by oxygen therapy at a time when the carbon dioxide regulated respiratory center is not functioning have been documented.[20,21] The promotion of adequate pulmonary lung ventilation by a mechanical body respirator serves to reduce blood carbon dioxide concentration during oxygen therapy without endangering the respiratory excursion or rate.[22]

The rationale and efficacy of carbonic anhydrase inhibition (Diamox) in this disorder has also received much recent attention in the literature. This drug has an effect on the carbon dioxide metabolism of the erythrocyte as well as an effect on urinary excretion. One or both of these actions may be related to therapeusis achieved.[23–25]

No discussion of papilledema and its association with polycythemia is complete without considering the evidence that hemangioblastoma of the cerebellum and even pressure in the area of the diencephalon may be associated with polycythemia. Because such lesions may not give other than air encephalographic evidence of their presence, this combination of findings must alert the physician to the possibility of an intracranial expanding lesion.[26,27]

SUMMARY

1. The pathologic changes in the lung produced by chronic lung disease predispose to the production of polycythemia and respiratory acidosis.

2. The increase in blood-formed elements and blood carbon dioxide concentration may result in increased intracranial pressure and papilledema.

3. The increased intracranial pressure and papilledema are probably related to the effect of carbon dioxide on the intracranial vasculature and effect of polycythemia on the viscosity of the blood. Increased jugular venous pressure accompanying chronic lung disease probably plays a minor role.

4. Therapy is directed toward reversal of the abnormal blood physiology.

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Occurrence of Lipemia in Experimental Allergic Encephalomyelitis

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ALLERGIC ENCEPHALOMYELITIS is produced experimentally in laboratory animals by the injection of various chemical fractions of brain and spinal cord. This condition is related both clinically and pathologically to certain demyelinating diseases of humans, such as the post-infectious encephalitides and the encephalomyelitis which sometimes follows rabies and smallpox vaccinations. The disease is of considerable importance because it closely resembles certain spontaneous demyelinating diseases[1,2] in humans for which no known etiologic agent has been discovered. Many animals have been found to be susceptible to the disease – monkeys,[3] cats,[4] dogs,[5] guinea pigs,[6] rats,[7] mice,[8] and rabbits.[9] The clinical course and the early stages of the disease as seen histologically are similar in all species. In the guinea pig the typical lesion is a vascular and perivascular inflammation. These animals have proved to be very satisfactory for study of the disease because of their marked susceptibility to injection of brain materials and because of the absence of spontaneous encephalitis.

Although many aspects of the disease have been studied, no previous reports have appeared on the blood chemistry of animals with allergic encephalomyelitis. The present report describes the results of an investigation of serum lipids and proteins initiated in connection with a study of the encephalitogenic activity of various chemical fractions of brain and spinal cord. The most striking biochemical manifestation of the disease observed in this study has been a marked elevation in serum lipids in many of the sick animals. The relation of this lipemia to the disease process and the changes in concentration of the lipids and proteins of the abnormal sera are the subject of this report.

MATERIALS AND METHODS

The guinea pigs used were adult males (500 to 800 gm.) of mixed color produced by random breeding in a closed colony maintained at the National In-

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stitutes of Health. After leaving the colony, they were observed for two or more weeks for evidence of spontaneous encephalomyelitis. In over a thousand animals tested, no spontaneous encephalomyelitis was found.

The material used for the production of experimental allergic encephalomyelitis was lyophilized whole guinea pig brain or a glycoprotein fraction prepared from bovine spinal cord.[10] Preparation of material for injection was as follows: 40 mg. of lyophilized brain (or bovine cord fraction) and 10 mg. of heat-killed tubercle bacilli (H37RV) were mixed in a glass homogenizer of the Elvehjem type; 2 ml. mineral oil, 1 ml. 0.85 per cent saline containing 0.5 per cent phenol, and 1 ml. melted aquaphor were added to the tube, and the mixture was emulsified until the solid material was completely dispersed. The mixture was then incubated one hour at 60° C. Intracutaneous injections of 0.1 ml. (=1 mg. antigen) were made with a short number 26 needle in the anterior neck region of the guinea pig. Smaller doses were made up by dilution of the homogenized mixture with more of the adjuvant prepared in the same manner without antigen. The technic was modified for large doses so that 1 ml. was injected subcutaneously.

Neurologic examinations for hind leg weakness and ability to return to normal stance after the animal was placed on its back were made two or three times a week. In addition, the animals were observed daily by the caretaker for gross signs of paralysis. At the end of 30 days, or when the animals became acutely paralyzed and were judged to be near death, they were anesthetized by an intraperitoneal injection of Nembutal and blood was obtained by heart puncture. The blood was allowed to clot and the serum was separated by centrifugation. The animal was perfused with buffered neutral formalin,* and the brain and spinal cord in the vertebral column were removed and stored in the same formalin solution for subsequent histologic examination. The blood serum was stored in a refrigerator at 5° C. until the necessary analyses were completed.

Paper electrophoresis was carried out on 0.01 to 0.07 ml. samples subjected to 90 to 100 volts with barbital buffer, pH 8.6 $\mu = 0.05$, for 17 hours. Protein staining was done according to the directions of Block, Durrum, and Zweig.[11] Lipids were stained with Sudan black by Swahn's method.[12] Because normal guinea pig serum lipids are very low, it was necessary to use 0.07 ml. of serum for satisfactory staining.

Serum lipid extracts were made by a modification of the Folch extraction procedure, according to Sperry and Brand.[13] The extracts were analyzed for total lipid, total and free cholesterol, and lipid phosphorus. Because several modifications have been made, the analytic procedure is described in detail.

Extraction. One ml. of normal serum (or 0.5 ml. of visibly lipemic serum) was pipetted into 19 ml. of a mixture of 2 volumes of chloroform and 1 volume of methanol. The solutions were left at room temperature for 30 minutes, shaken occasionally, and then filtered into 25 ml. glass-stoppered graduates. The filtrates were made up to volume by carefully washing the papers with a small amount of the 2:1 $CHCl_3$-CH_3OH solution. Five ml. of water were added and

* 8 gm. $NaH_2PO_4.H_2O$, 16.7 gm. $Na_2HPO_4.7H_2O$, 200 ml. 37 per cent formaldehyde diluted to 2000 ml. with distilled H_2O.

the two phases mixed thoroughly. The emulsion was broken by centrifugation for 10 minutes at 1500 r.p.m., and aliquots of the lower layer were carefully removed for analysis by means of a Wintrobe pipette. From normal serum extracts, 3 ml. aliquots were used for phosphorus, free cholesterol, and total lipid determinations, and 2 ml. for the determination of total cholesterol. Smaller aliquots, 1 to 2 ml., sufficed for analyses of extracts from lipemic sera. The solvent was completely removed under a nitrogen stream at 60 to 65° C. Tubes for total lipid determination were placed in a 65° C. vacuum oven for an additional half-hour to remove the last traces of solvent.

Total lipid. For determination of the total lipid Bragdon's procedure[14] was followed, except that 5 ml. of the dichromate reagent were used and diluted to a final volume of 12.5 ml. The color was read at 580 mμ in a Beckman model B spectrophotometer equipped with an adapter for 15 mm. test tubes. The "total lipid" values were derived from a curve based on cholesterol as the standard lipid.

Lipid phosphorus. The phosphorus content of the lipid extract was determined by a modification of the Fiske-Subbarow method[15] as follows: After evaporation of the solvent, the digestion was carried out with 10 N H_2SO_4 and 30 per cent H_2O_2. For color development 1.25 per cent ammonium molybdate and 0.125 per cent aminonaphtholsulfonic acid in a mixture of sulfite-bisulfite were used. The sensitivity of the method was enhanced by heating the tubes 10 min. at 100° C. immediately after the reagents were added. The stable color obtained was compared with the color of a standard solution of KH_2PO_4 at 660 mμ.

Cholesterol. The total and free cholesterol were determined as described by Zak and co-workers[16] and Brown and co-workers.[17] Free cholesterol was precipitated as the digitonide. It was found that satisfactory precipitation and clarification of the solution in the free cholesterol determination required the addition of 3 to 4 drops of 30 per cent $AlCl_3$ prior to addition of the digitonin solution.

Total protein. This was determined colorimetrically by the biuret method of Weichselbaum.[18] Colorimetric readings were made at 540 mμ in a Klett-Summerson colorimeter. Pooled normal human serum was used for preparation of a standard curve, the values of which were obtained by micro-Kjeldahl determination. Similar results were obtained with weighed amounts of pure human albumin.*

Glycoprotein determination. Protein-bound carbohydrates were determined by a method based on the work of Badin and co-workers.[19] One-tenth ml. of serum diluted one to three with 0.9 per cent NaCl was added dropwise to 10 ml. of cold absolute ethanol in a 15 ml. centrifuge tube and left in the refrigerator overnight. It was then centrifuged and the precipitate washed twice with 80 per cent ethanol to remove all traces of free sugars. After the precipitate was dissolved in 1 ml. of distilled water, the analytical procedure was carried out as described by Roboz and co-workers.[20]

Histologic examination. Midsagittal and parasagittal sections of the cerebrum, brainstem, and cerebellum, and midsagittal sections of all or most of the

*Kindly supplied by Dr. Douglas M. Surgenor of the department of physical chemistry, Harvard University School of Medicine.

spinal cord were prepared and stained by hematoxylin and eosin. Upon subsequent microscopic examination, the presence or absence of typical meningo-encephalomyelitis was determined, as described by Alvord and Stevenson.[21] The intensity of the pathologic reaction was graded as follows:

++ Large inflammatory reactions about blood vessels easily seen (x30) in almost all microscopic fields.
+ Similar reactions seen in several microscopic fields, or smaller reactions seen in many fields.
± Small inflammatory reactions seen in only one or a very few fields.
? Small focal accumulations of leukocytes (lymphocytes and as yet poorly identified cells) in the leptomeninges only.
0 No abnormality seen.

Separate grades were given to the brain and spinal cord. Generally, the brain and spinal cord contained similarly severe inflammation, but occasionally one or the other was more strikingly involved. The more severe grade was accepted as probably correlating better with the clinical observations and was used in the assignment of a numerical index of the severity of the disease[22] as follows:

		Clinical Score		
		O, ?	+*	*K or D***
Histologic Score	*O, ?*	0	0	1
	±	1	2	3
	+, ++	3	4	5

* + = definite paralysis.
** K or D = severe paralysis leading to death or requiring terminal sacrifice before 30 days.

RESULTS

Data presented in the first three tables show a high correlation between the incidence of encephalomyelitis and of lipemia in guinea pigs injected with various amounts of active material. The correlation between the pathologic condition and lipemia can be demonstrated in two ways. All the animals studied (regardless of material injected) were rated on a graded response scale based on a combination of neurologic and histologic evaluations. These individual evaluations were then compared with the presence or absence of lipemia. If there were no pathologic symptoms (disease index = 0), the incidence of lipemia was very low. As the severity of symptoms became more marked, the incidence of lipemia increased to 59 per cent in animals showing maximal response to the injection (table 1).

The same correlation is apparent when the incidence of lipemia is related to the dose of injected lyophilized brain (table 2). The percentage of lipemic samples is based on visible lipemia and thus takes into account only those samples in which the lipid had increased more than two or three times the normal value. It is noteworthy that the abnormal blood condition does not require whole brain injection, but is produced also by a glycoprotein prepared from bovine spinal cord[10] (table 3).

The number of animals represented in these tables is around 300, but at the present time over 1000 animals have been tested with various fractions and we have never found any deviation from this high correlation between the two conditions. Lipid analyses of sera from normal and abnormal animals are presented in table 4. Because of the great variations observed in a given series of abnormal animals, the individual values are presented rather than an average value for the series. These animals received sufficient lyophilized brain to cause a maximal response to the injection. All animals in the first group became acutely ill before the end of the

TABLE 1
INCIDENCE OF LIPEMIA IN RELATION TO SEVERITY OF DISEASE REACTION IN ENCEPHALITIC GUINEA PIGS

*Disease Index**	*Number Examined*	*Number of Lipemic Sera*	*Incidence of Lipemia*
			Per cent
0	79	4	5.1
1–2	25	6	24.0
3–4	63	18	28.6
5	112	66	59.0
Total	279		

*Increasing numbers indicate increasing severity of neurologic and histologic reactions.

30-day experimental period, and all showed intense histologic lesions. In each series analytic data were obtained on six of the ten animals injected. In the first group the total lipids of all six animals were elevated, but only four would have been rated lipemic by visual examination.

The cholesterol and phospholipid values of animals 632 and 636 are within the normal range. In the second group the one animal which failed to develop lipemia also failed to exhibit signs of severe paralysis.

The tendency for increase in phospholipid and cholesterol to lag behind the total lipid rise is also illustrated in table 5. Nine selected lipemic samples were compared with a normal series. The abnormal samples were selected because of their lipemic appearance, but were not all from animals receiving the same active fraction. These animals became acutely ill two to three weeks after injection, and their encephalitic condition was verified by histologic examination.

Although phospholipid and cholesterol content both increase markedly, their combined rise does not account for the total lipid increase. As a result, the ratios of phospholipid and cholesterol to total lipid decrease. A large part of the

TABLE 2
INCIDENCE OF LIPEMIA IN GUINEA PIGS INJECTED WITH LYOPHILIZED GUINEA PIG BRAIN

Lyophilized Brain	*Number of Animals*	*Clinical Symptoms*	*Positive Histologic Lesions*	*Disease Index**	*Visible Lipemia*
(mg.)		*(Per cent)*	*(Per cent)*		*(Per cent)*
Subcutaneous injection					
55	20	100	95	4.7±0.2	69
25	10	90	90	4.3±0.4	62
15	10	100	—	—	55
5	10	100	100	4.8±0.2	62
1	10	100	100	4.8±0.2	50
0**	10	0	0	0	0
Intracutaneous injection					
1	20	100	100	4.3±0.3	55
0.1	10	100	80	3.3±0.6	33
0.01	10	20	10	0.5±0.5	0

* Mean ± standard error of the mean.
**Adjuvant plus tubercle bacilli but no brain.

TABLE 3
INCIDENCE OF LIPEMIA IN GUINEA PIGS INJECTED WITH BOVINE GLYCOPROTEIN FRACTION

Bovine Cord Glycoprotein	*Number of Animals*	*Clinical Symptoms*	*Positive Histologic Lesions*	*Disease Index**	*Visible Lipema*
(mg.)		*(Per cent)*	*(Per cent)*		*(Per cent)*
Subcutaneous injection					
5	10	100	100	5	50
2.5	10	90	100	4.1±0.5	55
1	10	70	100	3.6±0.4	14
0.75 (dialyzed)	10	90	70	2.8±0.7	57
0.2	10	90	80	3.7±0.6	14
Intracutaneous injection					
0.02	10	40	50	2.0±0.7	20
0.002	10	0	0	0	0
1**	10	0	0	0	0

* Mean ± standard error of the mean.
**Adjuvant and killed tubercle bacilli omitted.

increased lipid is undoubtedly neutral fat. Studies are now in progress to determine whether or not some other lipid, not present in normal serum, occurs in the lipemic sera. Another change in the lipid partition of the abnormal samples is an increase in the ratio of free to total cholesterol.

In addition to lipemia in the encephalitic animals, changes were also found in the carbohydrates associated with serum proteins. These results are presented in table 6. It was found that the total protein and protein-bound carbohydrates were significantly increased in lipemic sera.

TABLE 4
SERUM LIPID VALUES — NORMAL AND ENCEPHALOMYELITIC GUINEA PIGS

Lyophilized Brain	*Animal Number*	*Disease Index*	*Total Lipid*	*Phospholipid*	*Cholesterol*	
					Total	*Free*
			mg./100ml.	*mg./100ml.*	*mg./100ml.*	
Subcutaneous injection						
1 mg.	631	5	5,340	652	267	157
	632	5	395	77	39	13
	634	5	843	158	65	30
	636	5	843	160	81	24
	637	5	479	58	39	9
	638	5	1,535	181	66	31
25 mg.	591	5	2,790	313	405	131
	595	5	2,790	280	183	98
	596*	3	222	39	51	—
	597	5	932	113	64	20
	598	5	532	80	32	8
	600	5	918	125	72	26
Normal (9 animals)**			200.4±18.0	43.9±3.7	44.8±1.8	8.6±0.6

* One of 2 animals in a series of 10 which did not show signs of paralysis. Both were rated ++, for the severity of histologic lesions.
**Mean ± standard error of the mean.

TABLE 5
SERUM LIPID RATIOS IN NORMAL AND LIPEMIC SERA

	Normal		*Lipemic*	
	*Average of 9 Values**	*Per cent of Total*	*Average of 9 Values***	*Per cent of Total*
	mg./100 ml.		*mg./100ml.*	
Total lipid	200±18.0		1,420 (800–2,100)	
Phospholipid	44±3.7	22	130 (76–207)	9 (8–13)
Total cholesterol	45±1.8	23	108 (66–244)	8 (5–12)
Free cholesterol	8.6±0.6	4	42 (20–76)	3 (2–4)
Free/total cholesterol	0.19		0.39 (0.24–0.52)	
Disease index	0		4.6±0.3	

* Mean ± standard error of the mean.
**Figures in parentheses represent the range of values in this series.

Paper electrophoretic technic was used for investigating the lipid distribution in normal and lipemic sera. Since the lipids occur in combination with serum proteins, determination of the lipids involved a simultaneous study of serum proteins. As shown in figures 1 and 2, the electrophoretic pattern of guinea pig serum is very different from that of normal human serum. The alpha-1 and alpha-2 globulins of human serum are clearly separated on the paper strip and their relative concentrations (per cent of total serum protein) are low compared with the guinea pig alpha-globulin. Under our experimental conditions, guinea pig alpha-globulin did not separate readily into alpha-1 and alpha-2 components. The relative concentrations of human beta- and gamma-globulins are higher than the corresponding guinea pig fractions. The lipoprotein patterns of the two sera are also different. In human serum the main lipoprotein fraction is found in the beta-globulin region, whereas in the normal guinea pig the main lipoprotein fraction is in the alpha-globulin region.

In the lipemic serum the beta-lipoprotein peak becomes very much exaggerated (figure 3), and in the extreme situation the lipid stain becomes a heavy black smear from the region of the alpha-lipoprotein back to the origin (figure 4). Also, in most of the lipemic samples, considerable lipid moves with the albu-

TABLE 6
SERUM LIPIDS, PROTEINS, AND GLYCOPROTEINS IN NORMAL AND ENCEPHALITIC GUINEA PIGS

	Number of Animals	*Total Protein**	*P*	*Protein-bound Carbohydrate**	*P*	*Total Lipids*
		mg./100ml.		*mg./100ml.*		*mg./100 ml.*
Normal	6	4,410±126.8		128±2.5		200
Minimal dose**	7	4,010±146.4	N.S.	121±7.8	N.S.	261
Maximal dose***	8	5,478±366.5	<0.05	157±6.8	<0.05	2,109

* Mean ± standard error of the mean.
** Disease Index = 0.7 ± 0.2.
***All 8 animals were sacrificed because of acute paralysis before the end of the 30 day period.

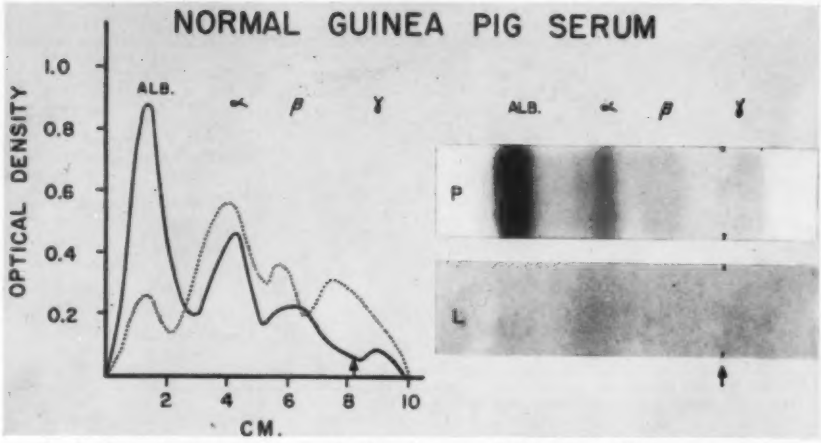

FIG. 1. Electrophoretic pattern of normal guinea pig serum. Protein (P)= solid line ———— (0.01 ml. serum). Lipid (L)=dotted line ---------- (0.07 ml. serum).

min fraction or slightly ahead of albumin.

The lipemic serum was studied further by a combination of centrifugation and paper electrophoresis. Before centrifugation, practically all of the lipids move in the electrophoretic field because of their combination with the serum proteins (figure 4). After centrifugation the major portion of the lipid is separated from the clear infranatant which contains the proteins. This lipid no longer moves in the electric field (figure 5). The speed of centrifugation (13,000 r.p.m., 4½ hours) was not sufficient to float the lipoproteins. Therefore, a small

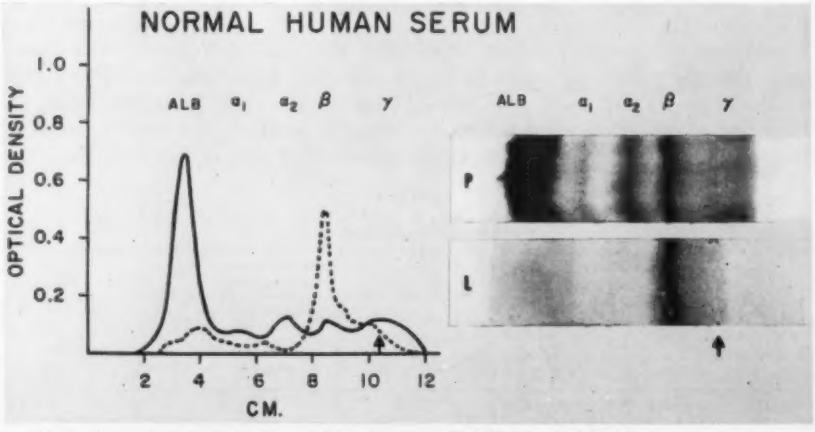

FIG. 2. Electrophoretic pattern of normal human serum. P=0.01 ml. L=0.04 ml.

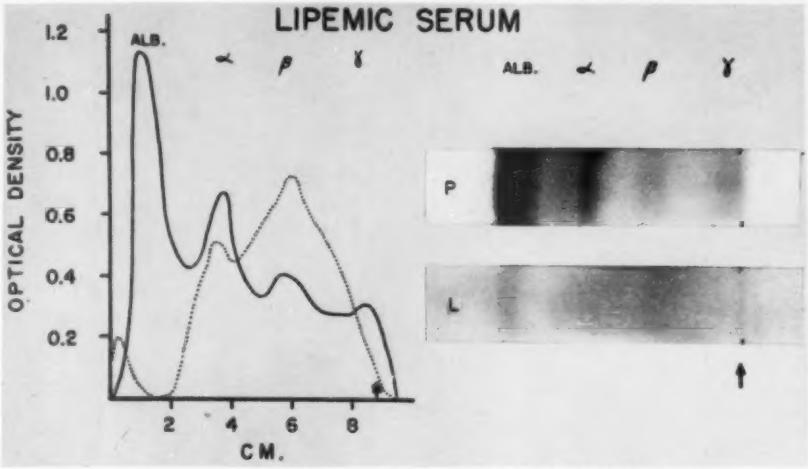

FIG. 3. Electrophoretic pattern of lipemic guinea pig serum. P=0.01 ml. L=0.04 ml.

fraction of the lipid remains in the infranatant (figure 6).

DISCUSSION

Experimental results with over 300 animals have shown a high incidence of lipemia in guinea pigs with allergic encephalomyelitis. Although the role of the encephalomyelitic agent in this lipemic condition is not yet clarified, it is certain that the active compound does not have to be lipid in nature. The fact

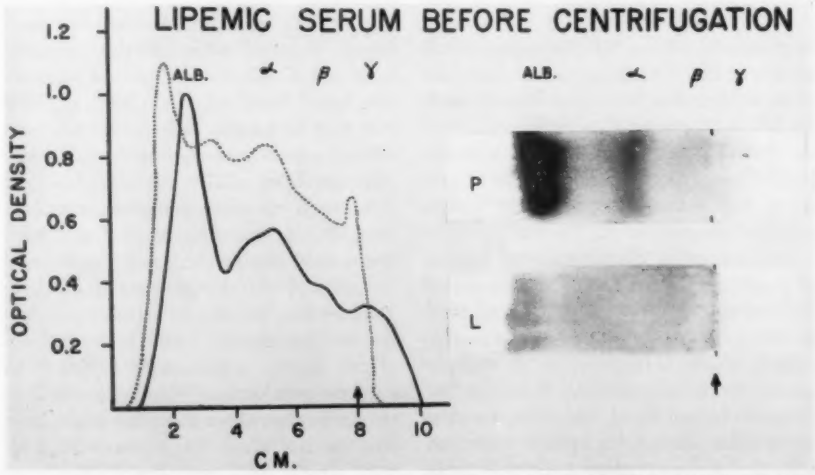

FIG. 4. Electrophoretic pattern of lipemic guinea pig serum before centrifugation. P=0.01 ml. L=0.02 ml.

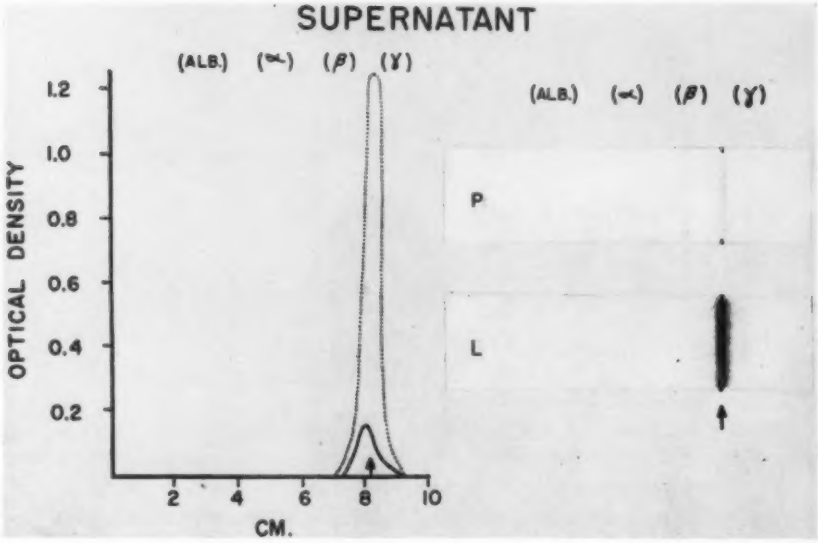

FIG. 5. Electrophoretic pattern of supernatant after centrifugation. P=0.02 ml. equivalent saline suspension. L=0.02 ml. equivalent saline suspension.

that a purified glycoprotein fraction prepared from bovine spinal cord also induces lipemia is evidence that the encephalitis and lipemia are not merely coincidental effects of the injection of whole brain. Other evidence that the same mechanism is responsible for both lipemia and encephalitis is derived from the fact that omission of killed tubercle bacilli from the injection mixture prevents the development of either pathologic condition.

The source of the high blood lipid is of considerable interest. The portion of the central nervous system most affected by the encephalitic process is the myelin sheath, which is largely lipid in composition. It is improbable that the increased blood lipid arises from the breakdown of myelin, since the total quantity of lipid present in the brain is not enough to account for the marked increases in the serum. The brain of a normal 600 to 700 gm. guinea pig weighs somewhat less than 4 gm. and about 320 mg. of this are lipid. If one assumes a blood volume of around 32 ml.,* it would take *all* of the brain lipid to increase the blood lipid level by 1000 mg./100 ml., and frequently values of 5000 mg./100 ml. of serum were found. Conversely, from lipid analyses of the brain of some of these same encephalitic guinea pigs, it has been found that the total brain lipid content was not significantly changed by the disease process.[23]

Since the increase in serum lipid cannot be directly attributed to breakdown of the myelin sheath, other possibilities must be considered. Histologic examination of organs other than the brain have shown no obvious abnormalities in

*Ancill (J. Physiol. 132:469, 1956) gives a figure of 43 to 45 ml. for a 600 to 700 gm. guinea pig.

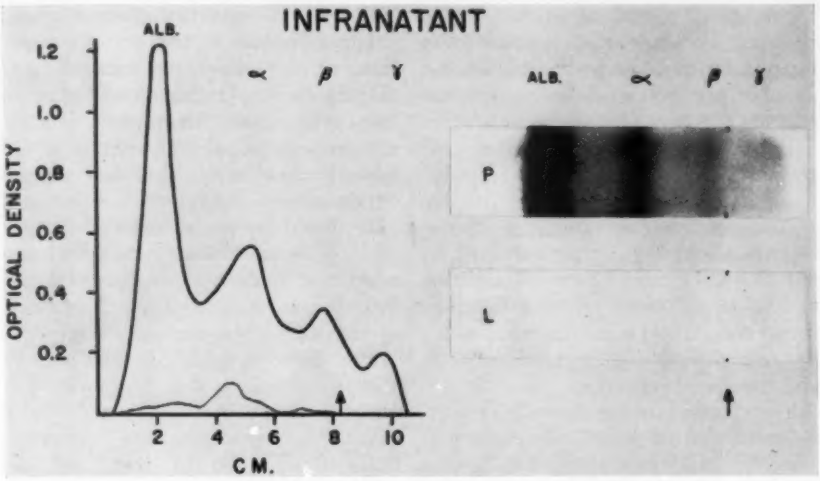

FIG. 6. Electrophoretic pattern of infranatant after centrifugation. P=0.01 ml. L=0.03 ml.

guinea pigs with experimental allergic encephalomyelitis,[24] except for fatty infiltration of the liver,* which would be expected with the high serum lipid levels observed in these animals.

One pathologic condition known to be accompanied by lipemia is experimental allergic nephritis. The nephrotic hyperlipemia is associated with a decreased plasma albumin,[25] whereas the encephalitic animals showed normal or increased serum protein content. There was no gross abnormality in the albumin component as determined by paper electrophoresis, in contrast to the almost complete depletion of serum albumin in nephrotic animals reported by Drabkin.[26] Therefore, it is concluded that the hyperlipemia reported here is unrelated to the nephrotic condition.

Another pathologic condition which is accompanied by elevation of serum lipids is diabetes mellitus. In the few cases which have been examined, the blood sugar of the lipemic guinea pigs was found to be normal.

Nervous control of fat mobilization and deposition has been proposed by several investigators. Experimental evidence has been presented by Beznak and Hasch[27] for changes in the fat depots in sympathectomized animals. Hausberger[28] has also observed changes in fat deposition following surgical denervation of the fat depots. The result of denervation was increased fat deposition in the cells. Schrade[29] concluded that regulation of lipid metabolism was under central nervous system control.

It is interesting to note that work of Korn[30] and Quigley[31] has demonstrated an enzyme, lipoprotein lipase, in adipose tissue. It is possible that such an enzyme could serve as an intermediary in the regulation of fat mobilization by the central nervous system. It has been suggested that the location of the lesions in

*We are indebted to Dr. Ilona D. Sibrik of Georgetown Medical School for examining the livers of the lipemic animals.

the brain or spinal cord controls the presence or absence of paralysis; the same factor could be responsible for the variable occurrence of lipemia in sick animals.

Even if we accept the concept of central nervous system control of an enzymatic mechanism for liberation or deposition of fat, our knowledge of the disturbance in the central nervous system caused by encephalomyelitis is rather limited; therefore, no exact interpretation can be given for the relationship between the distribution of the lesions and the lipemia observed.

Experimental encephalomyelitis is considered to be an allergic manifestation. There is some evidence from the literature that allergic conditions affect the concentration of the protein-bound carbohydrates of serum.[32] Because of this, the increased glycoprotein content of these lipemic sera is of special interest. Weimer and co-workers[32,33] have observed a significant increase in the carbohydrates bound to serum proteins in experimental tuberculosis in guinea pigs. In Brucella-infected rabbits, gamma-globulin carbohydrate was likewise increased, and the authors attributed this increase to antibody formation. Although the fraction of carbohydrate bound to gamma-globulin has not yet been investigated in encephalitic guinea pigs, some evidence has been obtained that the injection of brain tissue plus adjuvant results in increased gamma-globulin in guinea pig serum and in the spinal fluid of rhesus monkeys.[34]

It is possible that demyelination may result from a defect in lipid metabolism rather than from a local allergic reaction. The brain lesion has been attributed to an antigen-antibody reaction occurring in the perivascular space following penetration of the blood-brain barrier by circulating antibody. However, a correlation between circulating antibody titer and the encephalitic condition has never been established. The present data do not preclude an allergic reaction as the causative mechanism; they only suggest an alternative approach to the problem.

It should be mentioned that Stadler and co-workers[35] have reported abnormal blood lipids in a few cases of Krabbe's disease, a demyelinating condition of man which appears to be of genetic origin. It is suggested by the authors that the nervous system degeneration in Krabbe's disease may be secondary and that the primary lesion may be a metabolic disorder. On the other hand, one of the present authors[36] studied the blood of several multiple sclerotic patients and did not observe any significant changes in serum lipids.

SUMMARY

Investigations have been carried out on the blood serum of over 300 guinea pigs with experimental allergic encephalomyelitis. As a result of this study, a new manifestation of the disease, lipemia, has been added to the classic syndrome consisting of ascending paralysis leading to death and characteristic perivascular lesions in the central nervous system.

A high correlation was found between lipemia and the severity of the disease as established by neurologic and histopathologic examination. About 60 per cent of the animals receiving maximal doses of whole brain or purified glycoprotein from bovine spinal cord developed lipemia. Serum lipid concentration increased from a normal value of 200 mg. per 100 ml. to as high as 5000 mg. per 100 ml. In the normal serum, phos-

pholipid and cholesterol account for about 45 per cent of the total lipid, whereas in the lipemic sera they account for only 20 per cent of the total lipid. Thus, the marked increase in total lipid is either increased neutral fat or neutral fat plus some lipid not normally present in serum. Further work on this phase of the problem is in progress. In lipemic sera, total protein and protein-bound carbohydrate are also elevated.

Although the mechanism by which the encephalitogenic agent induces lipemia has not been clarified, it is certain that the active compound does not have to be lipid in nature. On the basis of positive results with a purified glycoprotein fraction from bovine spinal cord, which induced the lipemia as well as the histopathologic changes, it has been concluded that the two manifestations of the disease are related.

The authors wish to thank Mr. D. W. Shaw of the National Institute of Mental Health for his skillful assistance with the animal experiments and the paper electrophoretic studies.

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■ In all cases of spinal meningitis, rest in the recumbent position, more or less strictly enforced according to the urgency or leniency of the symptoms, is indispensable, the best position, perhaps, being not strictly on the back, but rather upon the side, and with the limbs a little lower than the back, so as to favour the draining away of blood from the congested parts,and at the same time, to facilitate the use of the local applications to the spine which may be necessary. Upon this point there can be little or no difference of opinion; upon all other points, in all probability, few will think alike. For my own part, I should be disposed to place most confidence in iodide of potassium and opium, with the local application of ice to the back in acute cases, and to bichloride of mercury, with counter-irritation in one form or other to the spine, in chronic cases. At the same time, I am inclined to think that the present fashion has set very unwarrantably against the old practice of giving calomel and opium, so as to affect the gums slightly and speedily, and of using local, if not general, bleeding in acute inflammatory disease. There can, I think, be little doubt as to the marked influence for good of calomel and opium in acute inflammation of serous membranes; and it would require very little persuasion to induce me to prefer this mode of treatment to that by iodide of potassium in acute spinal meningitis.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Gelastic Epilepsy

David D. Daly, M.D. and Donald W. Mulder, M.D.

THE POSSIBILITY that emotion may be a manifestation of an epileptic seizure was recognized by several early writers. Hughlings Jackson[1] wrote of "fear which 'comes by itself'—the *symptom fear*," and he felt that the emotion represented an integral part of the seizure. Sir William Gowers[2] also commented upon emotion as an aura in ten of his patients. Oppenheim,[3] in speaking of epilepsy, remarked: "Terror, shuddering, depression, gayety, rage, or recollections of some previous event in his life, etc., constitute the *psychic aurae*." Penfield[4] acknowledged that emotion may be a part of seizures, but emphasized that it is always an unpleasant emotion and added: " . . . other emotions, such as anger, joy, pleasure, sexual excitement, have never been reported by our patients as results of local cortical seizures or stimulation." Bonnet and Courjon[5] wrote of paroxysmal feelings of anguish and of other sensations which are often difficult to describe, but none of which were pleasant.

Manifestations of emotion during periods of automatic behavior came to the attention of both Jackson[6] and Gowers.[2] They commented that violence and rage may occur during such episodes, but both authors regarded these as examples of postepileptic automatism. Jackson[7] suggested that the behavior of patients in postictal automatism might be manifestations of their basic personality. Gowers[2] observed: "The emotional display is sometimes with a more cheerful character. One patient always laughed and sang for a few minutes after each attack of petit mal, and in another, a girl of 20, each slight seizure was followed by a paroxysm of kissing."

Laughter which occurs during seizures seemingly has received little attention in later times.* Wilson[8] mentioned "two instances of epilepsy with compulsive and unrestrained laughter as an aura," but gave no further details. We have observed two patients in whom laughter appeared to constitute a fixed part of the seizure pattern and have coined the term, "gelastic epilepsy," to emphasize that laughter characterizes their attacks.

REPORT OF CASES

Case 1. An 11 year old boy had been subject to seizures for three months. These would begin without warning. His parents noted that he would suddenly begin to stare, and that his face would flush. His head would then turn to the left. On several occasions, when he was

*Since this paper was submitted for publication, Druckman and Chao have reported several cases of laughter as an epileptic phenomenon. (Druckman, R., and Chao, D.: Laughter in Epilepsy. Neurology 1:26, 1957.)

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FIG. 1. A discrete area of calcification in the left temporo-occipital region of the patient in case 1.

standing, he would turn entirely around in a counter-clockwise direction. Throughout this time the patient would laugh. The period of laughter might last from half a minute to several minutes. After the attack the patient would be confused, and appeared to have difficulty in finding words.

Results of a general physical examination were normal, as were the optic fundi. Neurologic examination disclosed nothing abnormal except for the visual fields, which were affected by right homonymous hemianopsia.

Roentgenograms of the skull (figure 1) revealed a calcification in the left temporo-occipital region; this was located just beneath the inner table of the skull.

The electroencephalogram showed irregular slow waves and occasional fast spikes arising from the posterior portion of the left hemisphere. At times there were paroxysms of rhythmic, bilaterally synchronous discharges at frequencies of about four cycles per second.

Hyperventilation consistently induced attacks, which could be observed in detail. The attacks began with sudden staring and unresponsiveness. Flushing of the face and dilatation of the pupils were seen. Almost immediately the patient's head turned to the left to such a degree that he seemed to be looking over his shoulder. Simultaneously, there was conjugate deviation of the eyes to the left. The patient then began to laugh in a most contagious manner. Motion pictures in sound were made of the attacks, and all who have seen them agree that both the sound of the laughter and the appearance of the patient are indistinguishable from the appearance of a normal person in laughter and the sound of normal laughter. In the attacks which were witnessed the laughter lasted from 60 to 90 seconds. The adversion of the head and eyes was sustained throughout the laughter. In one attack the laughter ceased momentarily while the patient sighed deeply and said: "Oh, dear!" As the laughter ceased, the patient would look about, but seemed confused and dazed. Careful testing disclosed consistent postictal aphasia lasting three to four minutes. When the patient was shown a common object, such as a pencil, a coin, a key, and the like, he would grope for the name of it and express annoyance by snapping his fingers and saying: "Oh, I know it." Once, when he was shown a book of matches, he could read aloud the printing on the cover but he could not tell what the matches were. Even when he was unable to name an object, he could often tell its use. As the aphasia resolved, the patient might approximate the name of an object, for example, by calling a wrist watch "a clock."

Surgical exploration revealed an infiltrating tumor in the left temporo-occipital region. The histopathologic diagnosis was mixed oligoependymoma.

Case 2. A 36 year old man had been subject to seizures for two years. The episodes would begin abruptly without warning. He had been told that he would stare and stop whatever he was doing. In some of the attacks he talked incoherently, saying such things as "We'll have to give it another test." In other attacks he did not speak. He would walk about, and during this time he would laugh.

The history was unremarkable except that, at the age of 14 years, he had been unconscious for several hours. The details of this incident were not known, nor was a cause for it ever determined.

A roentgenogram of the skull disclosed no abnormality. The electroencephalogram made while the patient was awake was low voltage in type. Infrequently, there were occasional discharges consisting of moderate voltage, rhythmic, six cycle per second waves. These appeared synchronously in both temporal regions. Another recording was made when the patient was asleep. At a depth of sleep which produced spindles in the tracing, random, irregular slow waves developed in the left tem-

poral region. Some of these slow waves had steep fronts. Rarely, sharp wave discharges occurred, intermixed with the slow waves.

Activation was carried out by the intravenous administration of 50 mg. of pentylenetetrazol (Metrazol) per minute. No effects were noted until 300 mg. had been administered. At this point, the patient was observed to begin smiling and then to laugh aloud. He opened his eyes, but would not respond. He laughed for about 90 seconds. During this time he spoke incoherently, saying that his name was "Eccles," which, in fact, it was not. Toward the end of the period the patient would respond to questions, but was disoriented. The confusion subsided rapidly and he appeared to be himself. The electroencephalogram during the seizure showed no evidence of focal discharge at the onset of the attack. A few seconds after the onset there was generalized, rhythmic, five cycle per second discharge, and then most of the recording became obscured by movement artifacts.

COMMENT

The observation of laughter during seizures in these two patients raises several points of interest. First, we may ask whether there is any cortical area, the functioning of which is associated with affect; that is to say, whether there is a specific cortical region which may constitute the anatomic substrate of emotion. Jackson[1] drew attention to the association of fear with epigastric sensation as the aura to an epileptic attack. However, he did not implicate any specific anatomic area as being involved in seizures associated with affect. Our studies[9] of patients with epigastric auras, as well as other visceral sensations, have led us to conclude that they arise from foci situated either in the frontotemporal region, including the insula, or from another area on the mesial parasagittal surface of the frontal lobe. We, too, observed that changes of mood often were accompaniments of seizures with abdominal manifestations. It will be noted that the anatomic areas mentioned constitute, so to speak, the poles of what has been termed the "limbic system" or "visceral brain." In recent years increasing attention has been devoted to this system, particularly by MacLean.[10] He summarized data based largely on animal studies, supporting the view that the limbic system is the major cortical area involved in the expression of affective behavior. These data need not be reviewed again now, but it is of interest to note that MacLean, by stimulation of the hippocampal area in animals, was able to produce "rapt attention or fearful alerting."

Most authors have emphasized that the emotions occurring as warnings of minor attacks are unpleasant. In our experience this is frequently, but not invariably, the case. In a previous study[11] we have commented that the aura to the attack, if it is affective in character, may be pleasant. Subsequent experience has confirmed this observation. Indeed, having learned to question patients carefully about such a contingency, we have encountered a number in whom a pleasant emotion constitutes a part of the early phase of the seizure. Therefore, in these two patients, the occurrence of laughter further confirms and extends these views.

An additional question arises: Is the laughter of these patients ictal, or is it possibly no more than a postictal automatism? We can supply no direct answer, since both patients were amnesic for the period of laughter. The problem of whether complex behavior for which the patient is amnesic constitutes an ictal or a postictal phenomenon is not new. Penfield and Jasper,[12] after an extended review of all their experience, both with focal seizures and the results of cortical

stimulation, concluded that automatic behavior may be ictal in character. We incline to the same conclusion with regard to our patients. In the second patient, the first clinical manifestation of the seizure was a smile which changed to laughter. In the first patient, the attack, clinically, was under way for a few seconds before laughter began. However, in this patient the laughter was associated with conjugate deviation of the eyes and adversion of the head. This was sustained throughout the period of laughter, suggesting continuing epileptic discharge in an eye-turning field. The evidence therefore would suggest that the laughter represented an ictal phenomenon. It has been suggested that the laughter in the first patient may represent a response to a visual or auditory hallucination, and that the head turning also was a manifestation of this. We regard this as an unlikely explanation, since one would anticipate that any visual hallucinations would find representation in the right homonymous field, and that any adversion of the head consequently would have been to the right, rather than to the left. We regard the adversion as an example of ipsilateral turning, a phenomenon we have observed on a number of occasions before. Laughter, while a complex motor phenomenon, is no more complex than the behavior that we have observed in other patients during ictal automatism.

We conclude that laughter may be a manifestation of epileptic discharge in the temporal region. Laughter is simply a facet of affective behavior. This would suggest that a wide gamut of emotional phenomena, both pleasant and unpleasant, may be manifestations of epileptic discharge within the temporal region.

SUMMARY

Two patients are described in whom laughter was a prominent part of focal seizures. The implications of these observations are discussed.

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Variations in Consciousness Produced by Stimulating Reticular Formation of the Monkey

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SINCE THE EARLY WORK of Magoun and Moruzzi[1] and others, attention has been focused on the reticular formation in the central nervous system. Recently it has been speculated, and some evidence obtained,[2] that this diffuse system is involved in maintaining the conscious state of the organism. During the past 15 years, one of the authors has been interested in the variations in consciousness which fall in the borderline epileptic states,[3,4] and another of the authors has observed the results of thalamic stimulation in cats.[5] We felt it would be of interest to determine if variations in consciousness could be produced by stimulation of various areas in the reticular formation. The Macaca mulatta was chosen as the experimental animal with this in mind. It is noteworthy that, in making observations on variations in consciousness, the experimental animal must be completely free from the effects of sedation of any kind.

METHOD

Monkeys approximately six months old were conditioned in the primate colony for four to six weeks to allow them to adapt to the handling necessary for psychometric testing. At the end of the period of adaptation, the animals were subjected to psychometric tests[6,7] as described later, and continued on daily testing six days a week until they reached a plateau of performance that did not vary significantly for a period of two to three weeks.

A crucial aspect of this experiment is the measure of the "state of consciousness" at any time. This state is inferred from a monkey's performance on a problem which has a known chance score. For example, in a situation where three choices are possible and only one choice is considered correct, any monkey has one chance in three of responding correctly. Thus, for a series of 16 problems, the chance score would be four. The number of correct responses over and above this chance score is considered due to the monkey's learned response. The number of responses must be great enough to prove statistical significance. We considered nine correct responses out of a series of 12 presentations in-

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dicative of the animal having "learned" the problem, since a score as high as this would be expected to occur by chance only one time in a hundred.

Prior to electrode placement and stimulation, the animal was taught the solution to a problem which involved the recognition of an unmatched object from a group of three objects For any group of 12 trials, two pairs of objects were used. For any given trial, the animal was presented with a tray on which were three objects. Two of these objects were similar, and the third, or odd, object covered an indentation in the tray in which was placed a piece of food, the reward for a correct response. The monkey must learn under which object the food is placed and to move that object to receive the reward. Seventy-two different types of objects were used. The odd object was placed in either of two positions, on the extreme right or left of the tray. The center position was always occupied by one of the similar objects. The position, right or left of the odd object, was also randomly predetermined. Thus, on a given trial, any one of two objects could be the rewarded object, and it could be either to the right or left. This method of presentation eliminated the possibility that the monkey learned a sequence of responses rather than the response to the odd object for only one trial. In other words, the animals learned to select the odd object rather than a certain position, such as right, or a pattern of positions, such as right, right, left, left. It should be noted here that a complete reduplication of a given group of 12 trials could occur after about 71 other groups of 12 were presented to the animal. This insured that the monkey learned to respond to the odd object rather than to any specific object.

The oddity problem described was used as a measure of the level of consciousness for only the last three monkeys tested. Prior to that time, the level was measured by a simpler problem, discrimination. In this test the animal was presented with only two different objects. The reward was always located under the same object. During a given series of 12 trials, the reward object was always the same and only its position on the right or left was manipulated. The positions were randomly predetermined. A reduplication series occurred only after the monkey performed in 35 other series with different objects.

The electrodes used were developed following correspondence with Dr. Delgado and consultation with Dr. Jasper. We have found that, for accurate place-

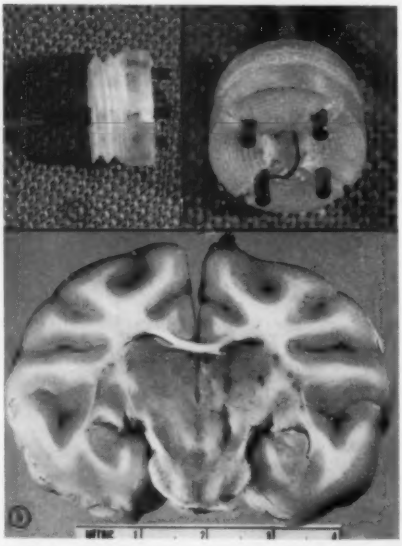

FIG. 1. The electrode.
FIG. 2. The connection between the electrode lead and metal jack.
FIG. 3. Coronal section of brain of monkey 6 with electrode in position.

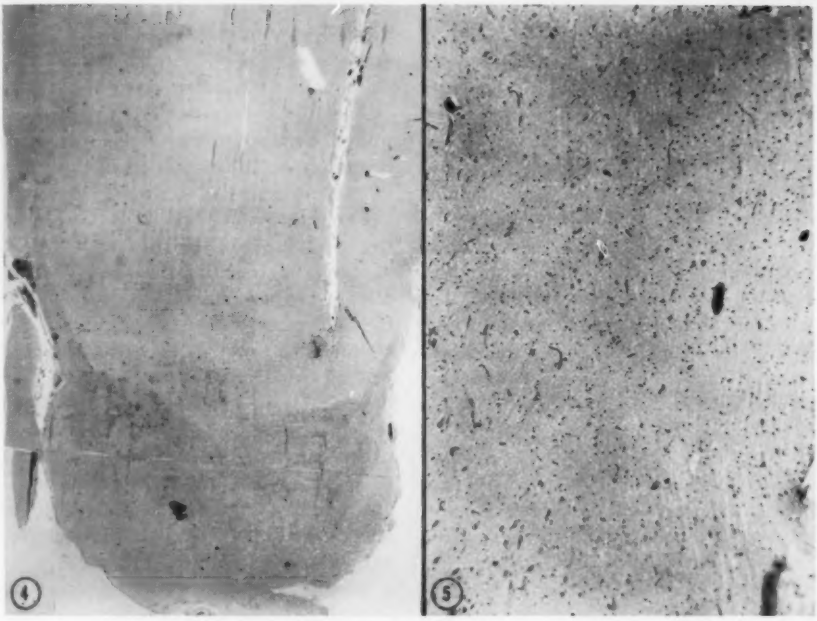

FIG. 4. Photomacrograph of midbrain, showing electrode tract.
FIG. 5. Photomicrograph of midbrain of monkey 6, showing needle tract to the right in the picture and the large motor-like cells of the red nucleus.

ment using the Horsley-Clark technic, a fine glass core approximately 0.7 mm. in diameter was the most satisfactory means of obtaining the necessary rigidity. For the final electrodes, four strands of enameled No. 50 stainless steel wire were wound about this core and the whole dipped in Tygon paint No. K-13. After drying and baking for 30 minutes at 300° F., the tips of the four wires were scraped clean, having arranged the position of the first three tips 2 to 7 mm. apart, the first tip being placed near the tip of the glass core. The fourth tip was placed at least 20 mm. from the first. The electrodes were tested for resistance and electrical leaks in a physiologic normal saline solution and were discarded if the resistance between any two electrodes in this solution exceeded 50,000 ohms or electrical leaks were present. The usual interelectrode resistance was 25,000 to 35,000 ohms. Ionization effects were controlled by frequent change of polarity. The electrode was sterilized by immersion for 30 minutes in 1/1000 solution of Zephiran. While the animal was under ether anesthesia, placement of the electrode was made through a burr hole, the position for which was indicated by the stereotaxic system. The burr hole was threaded to take a threaded lucite button which was drilled for four small metal jacks. These jacks consisted of 2 mm. of No. 24 stainless steel hypodermic needle barrel. The electrode and posi-

tions of the jacks in the lucite button are shown in figures 1 and 2. The center of the lucite button was drilled to allow the leads from the four electrodes to emerge. After removal of the enamel, the cleaned end of each wire was placed in its appropriate hole and the metal jack was driven in to jam it between the metal sides of the jack and the lucite walls of the jack hole. Connections were made to these jacks by means of 5 mm. sections of No. 25 stainless steel hypodermic needle barrel which were welded to electroencephalograph electrode lead wires. The usual resistance between electrodes 3 to 4 mm. apart in the brain substance of our monkeys was 45,000 ohms.

Placements of the electrodes were confirmed by microscopic examination following postmortem sectioning of the brains. Figure 3 is a photograph of the coronal section of the brain of monkey 6 at the level of the mesencephalon, showing the electrode in situ. Figure 4 is a photomacrograph of the midbrain area about the electrodes, and figure 5 is a photomicrograph of the area adjacent to electrode 1 and shows the large motor-like cells found in the magno cellular portion of the red nucleus. One or more electrodes in monkeys 3, 5, 6, and 8 were in the mesencephalic area. In monkey 4 the placement was near the medium raphe of the pons, and in monkey 7 the placement was in the region of the anterior hypothalamic nucleus. The exact locations of the electrodes in the six monkeys are shown diagrammatically in figure 6.

Anatomically the reticular formation is not sharply defined.[8] There is general agreement, however, that the system extends from medulla through the pons and mesencephalon, and it seems that areas in the thalamus and hypothalamus are at least functionally related if not an integral part of it. With this concept of the reticular formation, it is evident from our anatomic examinations that at least one of each set of electrodes was in, or bordering on, some portion of this reticular formation.

The electrodes having been placed, the monkey was tested psychometrically 48 hours after this procedure to determine if it continued to perform at its previous plateau. The next day a pseudostimulus (no actual electrical impulse) was given as a control measure and the psychometric tests were repeated. When the animal showed no change from his previous psychometric plateau, bona fide stimuli were given according to the various parameters noted in our table of observations. The Grass stimulator No. S4B was used in all experiments and a monophasic square top impulse was employed. Electroencephalograms were obtained before and approximately 48 hours after the placement of the electrodes and on several other occasions before the animal was sacrificed. Attempts were made to obtain an electroencephalographic recording from both depth and scalp electrodes immediately following stimulation, but blocking proved an insurmountable complication. Thirteen electroencephalograms were obtained from six monkeys in which electrodes were implanted within the brain. The animals were not under the influence of anesthetics or sedatives; they were awake in a quiet, dark room. Recordings between scalp electrodes placed on the occipital regions during quiescent periods revealed nine to 11 per second waves, with amplitudes varying between 20 and 60 mcvs. Scattered 15 to 25 per second waves were seen fre-

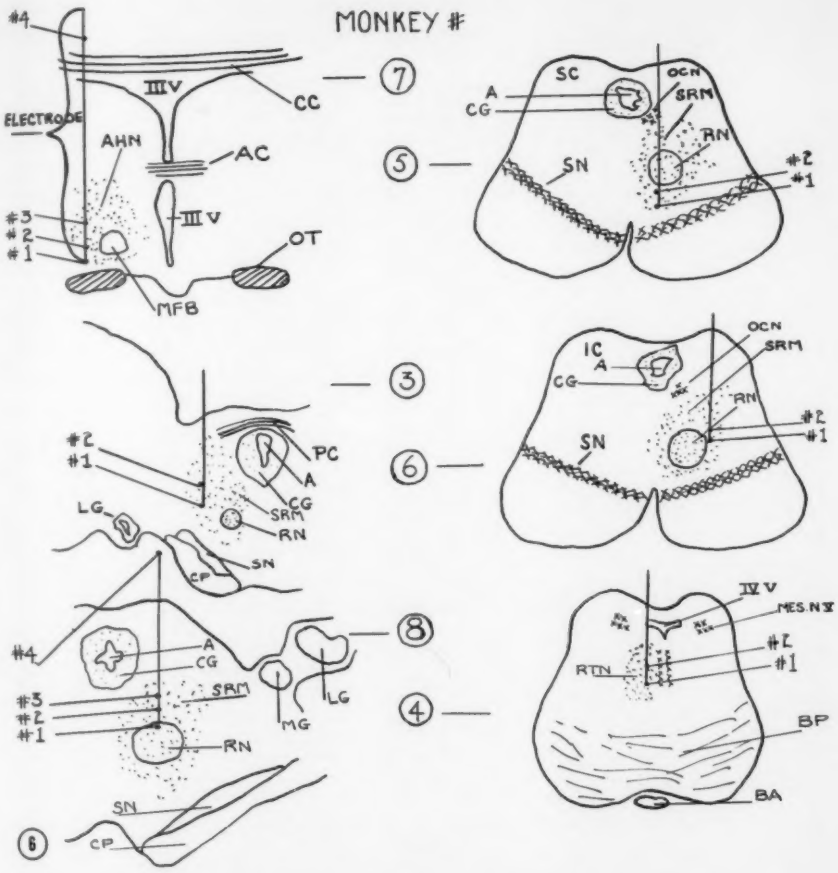

FIG. 6. Diagram of electrode placement. A—aqueduct; AC—anterior commissura; AHN—anterior hypothalamic nucleus; BA—basilar artery; BP—basis pedunculi; CC—corpus callosum; CG—central gray matter; CP—cerebral peduncle; IC—inferior colliculus; LG—lateral geniculate body; MESNV—mesencephalic trigeminal nucleus; MFB—median forebrain bundle; MG—medial geniculate body; OCN—oculomotor nucleus; OT—optic tract; PC—posterior commissura; PUL—pulvinar of thalamus; RN—red nucleus; RTN—reticular tegmental nucleus; SC—superior colliculus; SRM—substantia reticular mesencephali; SN—substantia nigra; III V.—third ventricle; IV V.—fourth ventricle.

quently, and low amplitude rapid frequency activity was observed, but it was difficult to discriminate this from extraneous potential sources. Activity from frontal and temporal regions appeared to be less well regulated and it consisted of a conspicuous number of scattered three to six per second waves.

Depth-to-depth recordings obtained from two monkeys on three occasions, the electrode points being 2 mm. or more apart, revealed patterns of waves of varying amplitudes and durations, of which rhythmic six to nine per second waves were most conspicuous. Superimposed upon these waves were seen continuous low amplitude rapid (20 to 25 per second) waves. In general, amplitudes recorded exceeded scalp to scalp recordings obtained at the same time. Occasionally brief episodes of ten per second waves were seen. It was noted that tracings derived from depth-to-scalp electrodes revealed higher amplitude activity than did scalp-to-scalp or depth-to-depth recordings, amplitudes as high at 300 mcvs. being obtained from depth-to-scalp electrodes. Rhythmic activity derived from depth electrodes appeared to be readily desynchronized to low amplitude rapid activity (25+ per second), with similar changes occurring simultaneously at the scalp electrodes when the animal was irritated (figure 7).

In one electroencephalogram obtained during a spontaneous tonic seizure in monkey 3, frequent high amplitude (300 mcvs.) repetitive sharp spike discharges were observed in recordings obtained from the depth electrodes and also from

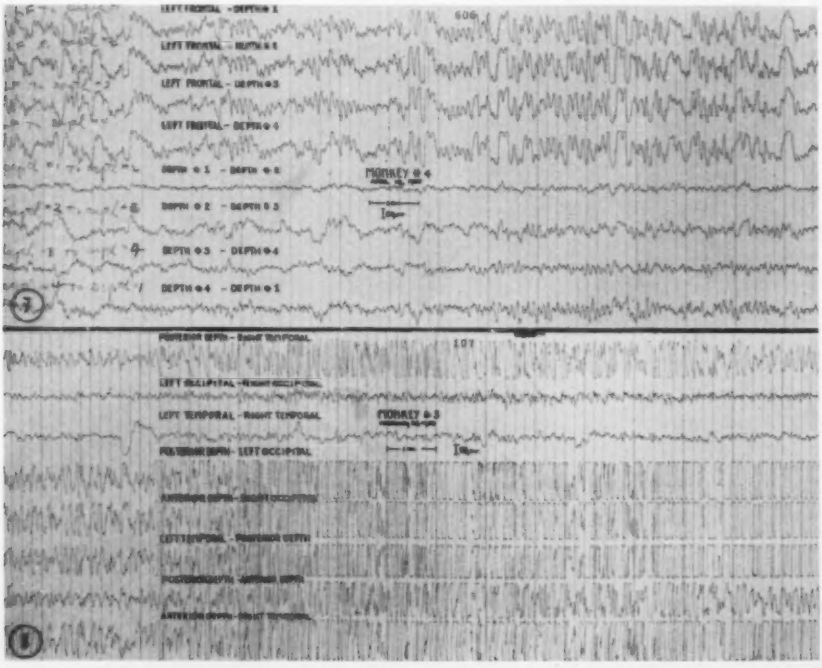

FIG. 7. Electroencephalographic record of monkey 4, showing the low amplitude, high frequency activity from channel 5 (interdepth electrodes) and slow-wave, high amplitude activity in depth and scalp electrodes.

FIG. 8. Electroencephalographic record of monkey 3 taken during spontaneous tonic convulsion. The high amplitude spike discharge is not reflected at the cortex.

depth-to-surface electrodes, but not from any scalp-to-scalp placements (the surface placements being left frontal to left occipital, right frontal to right occipital, left occipital to right occipital, left frontal to right frontal). It was observed from phase and amplitude relationships that the discharges arose closest to a depth electrode later found to lie in the mesencephalic reticular formation at the level of the lateral geniculate body (figure 8). It is suggested that the descending reticular formation alone was involved in this discharge.

OBSERVATIONS

Our observations are summarized in tables 1 and 2. Interelectrode stimulation was used in all animals except monkey 3. It should be noted that monkeys 3, 5, and 7 were tested with parameters of stimuli which produced motor components in their response. However, except for our first monkey in this series (monkey 3), the stimuli were varied until no motor response occurred, and thus a motor dysfunction was probably not a contributing factor to impairment of function in the performance of the psychometric tests. Monkey 4 was subjected to a control stimulus, using a lip electrode to either parietal or occipital scalp electrodes to observe the effect on performance of the unpleasant sensation and local twitching. The animal's psychometric performance was unchanged from the pre-stimulus performance. Thus any local sensory component on stimulation apparently had no significant effect on the psychometric performance of the animal. In the first four animals (monkeys 3, 4, 5, and 6) the psychometric tests were done immediately following the stimulus period. It will be seen that the response, measured either quired to complete the identical test done prestimulus, demonstrated a significant impairment of the psychometric performance. Monkey 5 also demonstrated the production of panic when the voltage was increased beyond 0.60. At 0.65 volts, panic first appeared, and extreme panic was evident on increasing the voltage to 0.90. Monkey 6 unfortunately developed an acute enteritis after the arrival of two new animals to our colony. We feel, however, that the production of yawning and sleep by interelectrode stimulation on five separate occasions and the ability to awaken the animal by merely increasing the stimulation by raising the voltage from 0.2 to 0.4 are worthy of note. The electrodes in this animal were located in the reticular formation adjacent to the lateral limit of the red nucleus, an area where degenerative changes have been reported in human patients having suffered from encephalitis lethargica.[9] Monkeys 7 and 8 have provided the most impressive results, since we decided to observe the psychometric response during stimulation in these animals. The animals were presented with the first choice within two seconds of commencing the stimulation and were allowed three seconds to make a selection. This proved to be a very practical test program, and control tests showed that the animals performed at their normal efficiency after at least 48 selections. An extinction test done on monkey 8 revealed that 42 trials (with no reward) over a period of 45 minutes were required to bring about extinction of this animal's learned response. Thus, the learned response was adequately maintained for our test periods.

Monkey 7 provided a means of assessing the critical features of the stimuli

TABLE 1

Monkey	Date	Horsley-Clark Coordinates		Location of Number 1 Electrode	Spacing of Other Electrodes	Electrodes Used and Resistance	Parameters of Stimuli		Clinical Response	Psychometric Response			Oddity or Discrimination Test		
										Correct	Incorrect	% Correct	Correct	Incorrect	% Correct
#3	10-22-54	Frontal Horizontal Lateral (Right)	—2.0 —2.5 —6.5	Mesencephalic Reticular Nucleus at level of right Lateral Geniculate Body.	#2 — 4mm. Above #1	#1 to right temporal scalp 30,000 ohms.	Frequency Delay Duration Voltage Stimulus for	=5.0 CPS =5.0 M Sec. =5.0 M Sec. =7.0 Applied —3 sec.	Left pupil dilated, left arm and leg twitched cry at end of stimulus. Approximately 15 min. after psychometrics completed had tonic spontaneous seizure during E.E.G.	Before stimulation			After or during stimulation		
										Discrimination test			After stimulation		
										5	0	100%	0	5(*)	0%
										Total time for each group of tests —30 sec.					
#4	10-25-55	F H L (right)	—0.3 —2.0 —4.0	Reticular Cell Mass near Median Raphe in Pons	#2 — 3 mm. above #1	#1 to #2 42,000 ohms.	F DE DU V Stimulus	=350 CPS. =5.0 M Sec. =0.2 M Sec. =1.0 applied for	No motor component or cry	Discrimination test			After stimulation		
										10	0	100%	6	4	60%
							7 sec. with 2 sec. rest for total of 69 sec.			Total time for each group of tests —59 sec.					
#4	11-29-55	Same		Same	Same	To lip and Rt. Occipital or Parietal Scalp	F DE DU V Stimulus for	=350 CPS =5.0 M Sec. =0.2 M Sec. =1.2 Applied —30 sec.	Right scalp and face twitched.	Discrimination test			After stimulation		
										10	0	100%	10	0	100%
										Total time for each group of tests —60 Sec.					
#5	12-13-55 (9:45 am)	F H L	=1.5 =3.0 =2.0	Reticular Nucleus below Red Nucleus (Mesencephalon)	#2 — 4 mm. above #1	#1 or #2 to Ipsilateral Occipital Scalp Electrode 15,000 ohms.	F DE DU V Stimulus for	=350 CPS =1.0 M Sec. =0.2 M Sec. =0.8 Applied —30 sec.	Smacking of lips right arm and leg flexed	Discrimination test			After stimulation 20 sec. after stimulation animal would not choose		
										5	0	100%			
#5	12-13-55 (10:00 am)	Same		Same	Same	Same	F DE DU V Stimulus for	= = same = =0.4 applied — 30 sec.	No motor component or smacking of lips	Discrimination test			After stimulation		
										5	0	100%	5	0	100%
										Total time for test 27 sec.			Total time for test 250 sec.		
#5	12-22-55	Same		Same	Same	#1 to #2 40,000 ohms.	F DE DU V Stimulus for	= = same = =0.6 applied —30 sec.	No motor component but several cries during 30 sec. stimulus period.	Discrimination test			After stimulation		
										Took single carrot in 25 sec.			Took single carrot in 130 sec.		
#5	12-22-55	Same		Same	Same	Same	F DE DU V	= = Same = =0.65—0.90	Extreme panic, dilated pupils, extremely restless appeared very frightened Tachycardia++ At 0.90V. Monkey to be at restraint no motor component.	Discrimination test			After stimulation		
										Took single carrot in 25 sec.			Took single carrot in 150 sec.		
#6 5 Separate stimuli this date. Animal has Gastro-enteritis (New arrivals to colony)	1-16-56	F H L (left)	=0.8 =3.0 =2.0	Reticular Nucleus (Profundus) of Mesencephalon	#2 — 2 mm. above #1 #3 — 4 mm. above #1	#1 to #3 45,000 ohms.	F DE DU V Stimulus for	= = Same = =0.2 Applied —30 sec.	Yawns and goes to sleep—eyes closed	Oddity test					
										Too unresponsive for tests					
		Same		Same	Same	Same	F DE DU V Stimulus for	= =Same = =0.4 Applied —2 sec.	Awakens sleeping animal.	Oddity test					
										Too unresponsive for tests					

*—Animal would not make a choice.

TABLE 2

for —2 sec.

*—Animal would not make a choice.

TABLE 2

Monkey	Date	Horsley-Clark Coordinates	Location of Number 1 Electrode	Spacing of other Electrodes	Electrodes used and Resistance	Parameters of Stimuli	Clinical Response	Psychometric Response: Correct	Incorrect	% Correct	Oddity or Discrimination Test: Correct	Incorrect	% Correct
#7	2-9-56	Frontal —8.0 Horizontal —5.0 Lateral —3.0 (right)	Tip of anterior Nucleus of Hypothalamus	#2 — 4 mm. above #1 #3 — 11 mm. above #1 #4 — 23 mm. above #1	#1 to #2 45,000 ohms.	Frequency =350 CPS. Delay =0.1 M Sec. Duration =0.2 M Sec. Voltage =0.8	Right pupil dilated to twice size of left No motor component.	Before stimulation Oddity test 12	0	100%	After or during stimulation During stimulation 6	6(1*)	50%
								Animals tested within 2 sec. of commencing stimulus and 3 sec. allowed for choice.					
#7	2-11-56	Same	Same	Same	#3 to #4 45,000 ohms.	F =400 CPS DE =0.1 M Sec. DU =0.2 M Sec. V =1.0		Oddity test 10	2	84%	During stimulation 11	1	92%
#7	2-11-56	Same	Same	Same	#2 to #1 45,000 ohms.	F = DE = same DU = V =	No motor or pupillary response	Oddity test 18	2	90%	During stimulation 4	16*	20%
#7	2-13-56	Same	Same	Same	#2 to #3 45,000 ohms.	F = DE = same DU = V =	No motor or pupillary response	Oddity test 10	2	84%	During stimulation 11	1	92%
#7	2-13-56	Same	Same	Same	#3 to #1 45,000 ohms.	F = DE = same DU = V =	No motor or pupillary response	Oddity test 10	2	84%	During stimulation 8	4	67%
#7	2-13-56	Same	Same	Same	#2 to #1 45,000 ohms.	F =350 CPS DE = DU = same V =	No motor or pupillary response	Oddity test 8	0	100%	During stimulation 0	8	0%
					Tested for Critical Parameters using Electrodes #2 to #1	F =250 — 400 CPS DE —0.01 — 0.2 M Sec. DU =Less than 2.0 M Sec. V =0.7 — 1.0							
No. 8	3-8-56	F —1.0 H —1.4 L (left) —4.0	Midbrain Reticular Nucleus Mid-Collicular level	#2 — 2 mm. above #1 #3 — 5 mm. above #1 #4 — 20 mm. above #1	#1 to #2 45,000 ohms.	F =350 CPS DE =0.05MSec. DU =0.2 M Sec. V =0.7	Head and eyes turned to left, and right foot flexed at ankle	Oddity test 7	3	70%	During stimulation 0	10	0%
#8	3-8-56	Same	Same	Same	#1 to #2 45,000 ohms.	F = DE = same DU = V =0.5	No motor components	Oddity test 4	1	80%	During stimulation 1	4	20%
#8	3-12-56	Same	Same	Same	#1 to #4 45,000 ohms.	F = DE = same DU = V =	No motor components	Oddity test 7	3	70%	During stimulation 7	3 (1*)	70%
#8	3-12-56	Same	Same	Same	#2 to #3 45,000 ohms.	F = DE = same DU = V =	No motor components	Oddity test 7	3	70%	During stimulation 2	8	20%
#8	3-12-56	Same	Same	Same	#1 to #3 45,000 ohms.	F = DE = same DU = V =	No motor components	Oddity test 6	4	60%	During stimulation 5	5	50%
#8	3-12-56	Same	Same	Same	#2 to #3 45,000 ohms.	F = DE = same DU = V =0	Control	Oddity test 9	1	90%	No stimulus		
#8	3-12-56	Extinction test— Allowing 6 sec. maximum for each choice, it required 42 trials over a period of 45 min. to bring about extinction of this animal's learned response.											

*Animal would not make a choice.

by correct responses or by total time reparameters as noted in table 2. Frequencies below 250 cps., delays above 0.2 seconds, and voltages above 1.0 increased the motor components in the animal's response. The use of four electrodes in the last two animals, with spacing 2 to 5 mm. apart for the first three electrodes and 20 mm. or more between electrodes 3 and 4, allowed assessment of the specificity of our response in terms of area of brain stimulated. Monkey 7 showed no significant impairment on stimulation between electrodes 2 and 3, and electrodes 3 and 4, using the same stimuli that reduced the animal's performance as low as 0 per cent when applied between electrodes 1 and 2. Stimulation between electrodes 1 and 3 gave an intermediate impairment of psychometric function (67 per cent of prestimulus correct response). This would indicate localization of the area giving maximum impairment of psychometric response to approximately 4 mm. (at least in vertical diameter) in the region of the anterior hypothalamic nuclei. We were unable to await complete psychometric plateauing of monkey 8, so that his prestimulus response varied between 60 and 90 per cent correct. With this feature in mind, however, there was no significant impairment of psychometric response on stimulating between electrodes 1 and 4, or 1 and 3, but the identical stimulus between electrodes 1 and 2 produced as low as 0 per cent of correct responses, and between electrodes 2 and 3, 20 per cent correct responses. In this animal the localization of the area giving maximum impairment of psychometric response was approximately 7 mm. (at least in the vertical diameter) in the region of the mesencephalic reticular formation at a level between the lateral and medial geniculate bodies. Incidentally electrode 4 in monkey 7 was located 23 mm. above electrode 1 and was in the white matter just below the posterior frontal lobe cortex adjacent to the superior sagittal sinus. Electrode 4 in monkey 8 was located 20 mm. above electrode 1 and was in the mesial parietal cortex.

DISCUSSION

Attention was drawn to the reticular formation when it was observed by chance that direct stimulation of this formation in the brainstem induced changes in the electroencephalogram similar to those observed on awakening from sleep, that is, activation, desynchronization, electroencephalographic arousal, and blocking reaction.[1] The region of the brainstem from which electroencephalographic arousal could be induced included the reticular formation and tegmentum of the lower brainstem, as well as the diencephalon and the subthalamus, together with the dorsal hypothalamus and ventromedial thalamus.

Hunter and Jasper[10] have reported "arrest phenomena" on stimulating the intralaminar system of the thalamus. This arrest phenomenon appears similar but not identical to the changes in consciousness we have observed in our animals. With the parameters of stimulation we used, the animals did not become "frozen," as reported by Hunter and Jasper, but rather appeared unable to perform a learned task. They could move about and eat food when it was placed in their mouths during stimulation. This type of response was obtained on stimulation over a wide area of the reticular system (from the anterior hypothalamic nucleus area to the reticular area in the pons). Knott and Ingram[11]

have reported a similar phenomenon on stimulation of either the intralaminar or anterior hypothalamic regions in the cat. Jasper[12] points out that the ascending reticular system may have an inhibitory component as well as an arousal or activating one, as he has shown that microelectrode stimulation of this system may cause an increase in the number and frequency of unit cell firing in the cortex, as in normal awakening or arousal. Stimulation of parts of the mesodiencephalic portions of the reticular system may, however, cause an arrest of unit discharge.

The critical features of parameters of stimuli and the need to localize stimulation to within a 3 to 7 mm. area to obtain significant psychometric impairment lend credence to the specificity of response to stimulation of discrete areas of the reticular formation.

It is interesting to note in monkey 6 that stimulation at a voltage of 0.2 in the mesencephalic reticular formation produced yawning and sleep, and that the animal could be awakened by simply increasing the stimulus voltage to 0.4. Are two different systems within the reticular formation involved in this case?

CONCLUSION

Stimulation of various areas in the reticular formation of the macaca mulatta produced a change in behavior which we infer is due to a change in the state of consciousness. We believe such a change in consciousness is not dissimilar to that seen in humans experiencing an epileptic episode of either the petit mal or a psychomotor variant type.

We are indebted to Professor Harry Harlow of the department of psychology, University of Wisconsin, who kindly arranged the training of our experimental psychologist.
We wish to express our appreciation to Dr. Jose Bebin of the University of Michigan for his assistance in confirming electrode placement by microscopic examination of brain sections. We are also indebted to Mr. Gordon Parkes, senior electroencephalograph technician, and Mr. Jerome Lukaszewski, experimental psychologist, of the Henry Ford Hospital for their assistance in this project.

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Cerebroautonomic and Myographic Changes Accompanying Induced Seizures

Jack M. Mosier, M.D., Philip White, M.D., Phyllis Grant, M.D., John E. Fisher, M.D. and Richard Taylor, M.D.

MUSCLE AND MOVEMENT ARTIFACTS have limited considerably the usefulness of the electroencephalogram as a diagnostic tool. This is especially true with activation procedures. The outstanding success of succinylcholine as a myoneural blocking agent in electroconvulsant therapy[1,2] suggested that this drug might be useful in electroencephalographic procedures. Pilot studies indicated that this may be a useful adjunct to the electroencephalographic laboratory. It also became obvious that this procedure would facilitate physiologic correlations of seizure activity, which is the basis of this report.

METHOD

The procedure evolved is as follows: 1) Atropine sulfate 0.4 mg. is administered intramuscularly one-half hour prior to the activations. 2) The patient is prepared with electrocardiograph leads from both wrists and an electromyograph lead to the left foot, with a needle electrode in the first interphalangeal space. A blood pressure cuff above the ankle is inflated to 250 to 300 mm. of mercury to prevent a myoneural block. 3) Succinylcholine in a 0.2 per cent solution is constantly dripped by vein to maintain clinical and electroencephalographic evidence of muscle paralysis. 4) Positive pressure 100 per cent oxygen inhalations are given concomitantly with succinylcholine drip. 5) Metrazol, 0.5 mg./kg. body weight/cc., is given into the succinylcholine tubing every 30 seconds near the needle until 20 cc. have been given. If no seizure occurs, Metrazol is given at the rate of 100 mg. every 30 seconds until one is produced. 6) Blood pressure is taken from the antecubital fossa in the standard way at 30-second intervals and recorded on the electroencephalogram by the technician. 7) As soon as the seizure ceases electrically, the succinylcholine drip is stopped and the patient is allowed to recover.

The patient is completely conscious until the seizure and can respond to questions by moving his left foot and toes. Initially, there is usually a mild rise in blood pressure; then the patient becomes accustomed to the mechanical breathing and his blood pressure and pulse rate stabilize. Some patients who receive excessive amounts of Metrazol

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Read at the eighth annual meeting of the American Academy of Neurology, St. Louis, April 29, 1956.

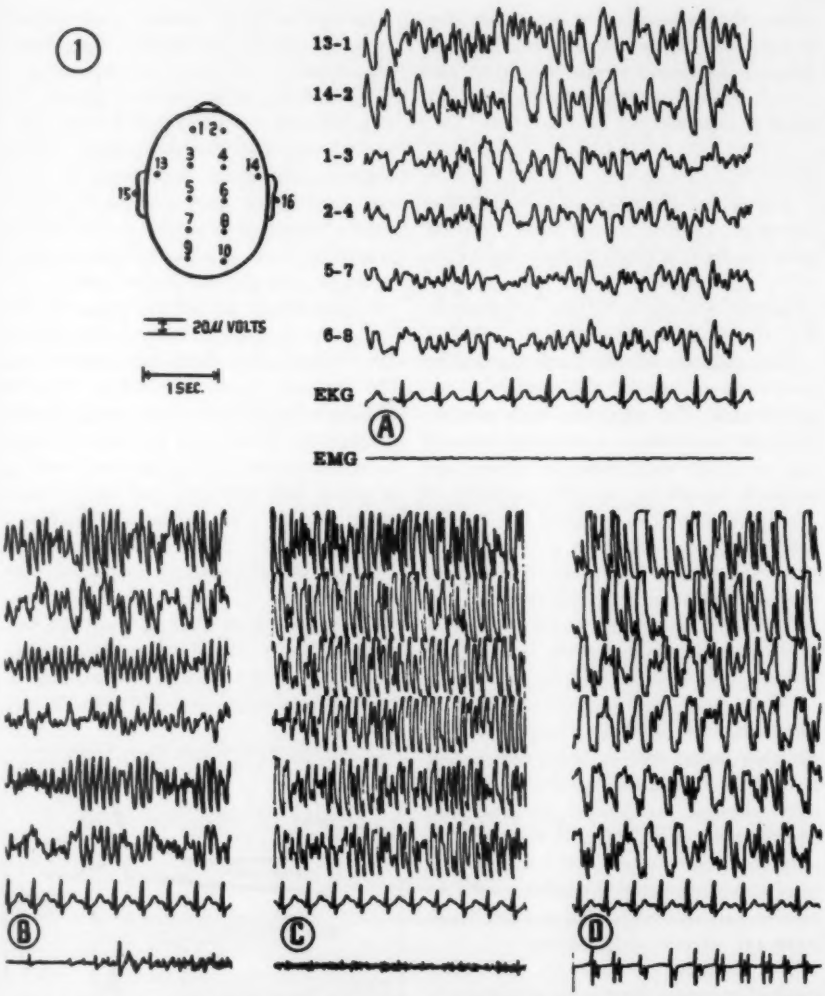

FIG. 1. Concomitant electromyographic and pulse changes associated with various phases of a generalized seizure. *A*, before seizure. *B*, onset of seizure. *C*, tonic phase. *D*, clonic phase.

(500 to 1,000 mg. or more) develop anxiety, increase in electroencephalographic amplitude, usually a tachycardia, and some further elevation of blood pressure. These occur shortly before a generalized seizure and are non-diagnostic, representing a Metrazol effect. These phenomena are somewhat unpleasant to the patients, who tell later of having felt dizzy, frightened, and having had other

indescribable unpleasant sensations. Approximately 65 per cent of the patients expressed a dislike of the procedure and a few definitely stated that they will not have it repeated.

RESULTS

A group of 41 patients (17 female and 24 male), ranging in age from 19 to 69, were studied. Clinically they were classified as idiopathic grand mal – 5, psychomotor epilepsy – 19, focal convulsive disorder – 15, and nonepileptic – 2.

The amount of Metrazol needed to produce a seizure by this method is approximately the same as with routine Metrazol activations and varied from 23 mg. to 2,453 mg. However, there are marked variations in the quantity of Metrazol needed to produce seizures on different days in a given patient.

As an average, we used 652 mg. of succinylcholine per patient, varying from 50 to 2,050 mg. In three patients, seizures were terminated with intravenous sodium Amobarbital 500 mg. because of their long duration (over 30 minutes). In these instances, respiratory depression lasted two to three and a half hours. All three developed mild pulmonary changes evidenced by fine and coarse moist rales. One of these developed an acute anteroseptal myocardial infarction during the procedure, with an uneventful recovery. Otherwise, there were no adverse side effects.

The duration of seizures with this method is longer than in spontaneous or otherwise induced seizures in the same patients. Presumably this is because of the ready availability of cerebral oxygen. This is in conformity with Gellhorn's studies.[3] The duration of the seizures was from 1' 10" to 63' 40", and the majority lasted less than five minutes.

Several seizure patterns are clearly seen by the succinylcholine and Metrazol technic. If a grand mal type of electroencephalographic pattern appears, the non-blockaded foot becomes tonic clinically, and the electromyogram shows repetitive, irregular, continuous 18 to 30 cps. oscillations, increasing in amplitude over a three to five second period. Simultaneously, there is a marked acceleration in pulse rate of from 50 per cent to 150 per cent over a ten second interval (one patient developed a sinus tachycardia of 192) (figure 1). Both the systolic and the diastolic pressures increase from 50 per cent to 100 per cent concomitantly (figure 2). There is a gradual decrease in hypertension and a gradual slowing of pulse rate (though still much faster than during the non-seizure period). The electromyograph usually ceases recording muscle activity from the foot ten to 20 seconds before the seizure activity stops. The electroencephalogram shows almost complete sudden extinction (figure 3). With the extinction, there occurs rapid slowing of pulse rate

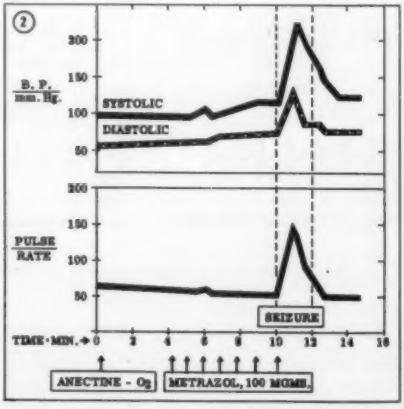

FIG. 2. Blood pressure changes associated with a generalized seizure.

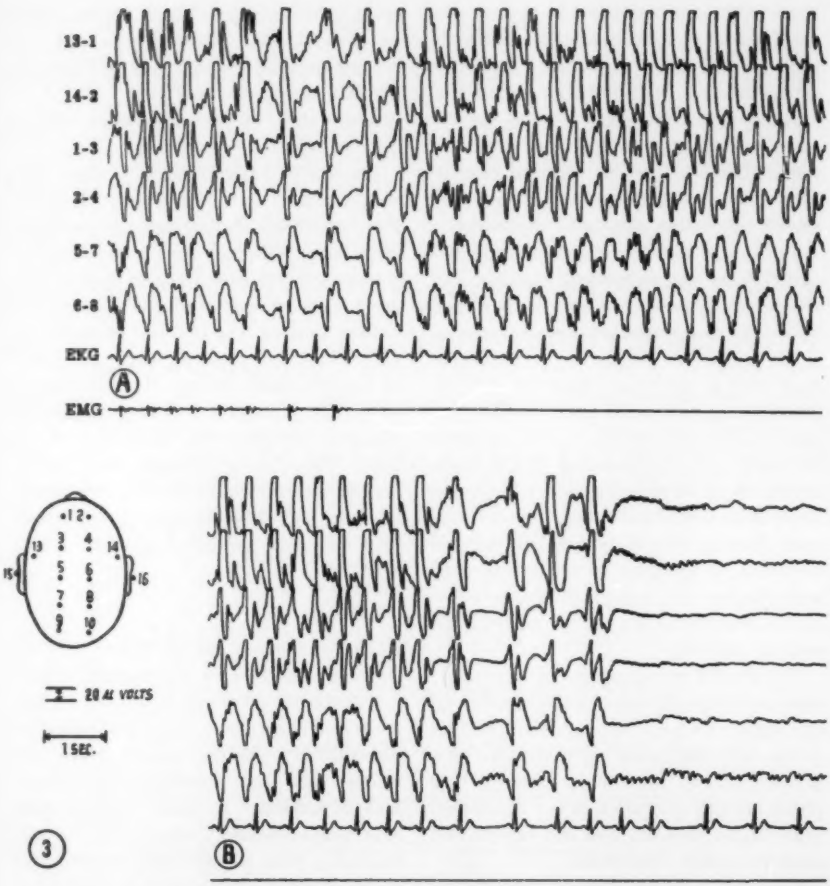

FIG. 3. The electroencephalographic, electrocardiographic, and electromyographic changes occurring at the end of a generalized seizure.

and rapid drop in blood pressure to preseizure values. In two patients who had spontaneous seizures while receiving succinylcholine but prior to the injection of Metrazol, the same events occurred.

The changes in blood pressure, pulse rate, and cardiac rhythm associated with convulsions either from Metrazol-induced seizures or electroconvulsant therapy are well known.[4,5] Lewis, Richardson, and Gehagen[2] concluded that the cardiovascular responses associated with electroconvulsant therapy were central in origin, but did not specify whether or not they were due to electrotherapy. Phiz-

ackerley and co-workers[6] indicated that objective evidence of cardiac dysrhythmias in a clearly established epileptic setting is rare. Wilson[7] mentioned that cardiac arrest can occur during spontaneous seizures. Jasper and Erickson[8] noted that a change in cerebral circulation never preceded, but always followed, excessive neuronal discharge.

In nine of the 41 patients, the electrocardiogram demonstrated cardiac arrhythmias. These consisted of auricular and ventricular premature contractions, short runs of bigeminy, ventricular tachycardia, and also short runs of bidirectional ventricular tachycardia (figure 4). The arrhythmia tended to occur during the clonic phase and ceased spontaneously in 30 to 50 seconds. Three patients with arrhythmia were retested and each showed a repetition of his previous response. In the generalized seizures the arrhythmias reverted to a sinus tachycardia before the extinction of electrical seizure activity.

The electroencephalograms showed 17 focal seizure patterns, mostly temporal in origin, but no cardiovascular changes were recorded until the patient progressed into a generalized seizure. Two psychomotor epileptics never developed generalized seizures and did not exhibit cardiovascular alterations.

Eighteen patients showed only generalized seizure activity, with the already-described cardiovascular changes.

Six of the patients developed diffuse, random two to four per second slow waves; these gradually appeared and gradually disappeared over three to four minute intervals. By inspection of the tracings, it was impossible to determine where this type of seizure started and where it ended. Cardiovascular and electromyographic changes were inconstant in this group. These patients with spontaneous or induced seizures displayed only alterations in consciousness, disturbance in memory, very slow mentation, and only occasional random movements.

Excessive salivation was the most troublesome autonomic manifestation that occurred during seizure activity; atropine minimizes this. In addition, piloerection, flushing, and perspiration were seen occasionally. Involuntary urination and/or ejaculation occurred in about half the patients toward the end of a generalized seizure. In one patient, hippus was observed during the clonic phase in rhythm with the clonus of the foot. The clonus stopped one minute and 40 seconds before the hippus ceased, whereas the latter stopped two seconds prior to electroencephalographic extinction.

DISCUSSION

The extinction of electrical activity signaling the end of a generalized seizure probably does not represent cortical neuronal exhaustion; we have recorded generalized seizures lasting from one minute and ten seconds to 63 minutes and 40 seconds. It seems unlikely that, in a single species (man), there would be such a wide physiologic range of neuronal stamina under similar conditions. It would be improbable for all cortical neuronal systems to become exhausted suddenly and simultaneously. Further evidence against sudden neuronal exhaustion is the fact that recovery from the hypertension, tachycardia, mydriasis, and muscle clonus occurred independently of each other and before there was any detectable change in the electroencephalogram.

It is suggested that, in generalized

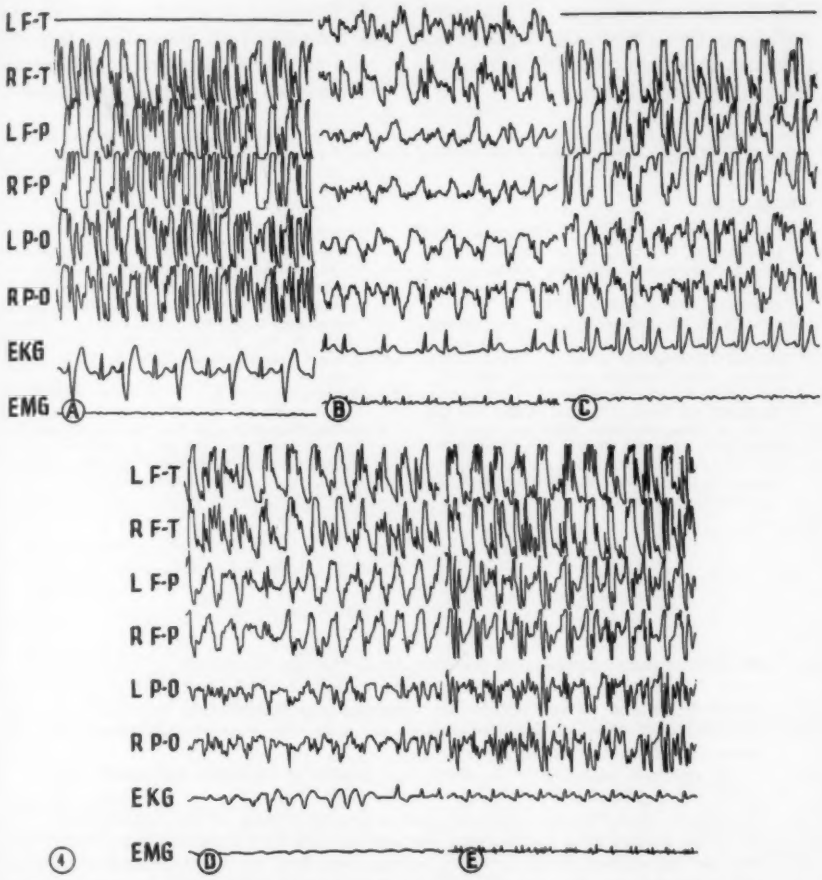

FIG. 4. The various cardiac arrhythmias associated with seizure activity. *A*, bidirectional ventricular tachycardia. *B*, frequent premature auricular beats probably occurring at the AV node with quick return to normal sinus rhythm. *C*, peaked T waves—nonspecific. *D*, ventricular tachycardia. *E*, elevated ST segments.

seizure activity, the tonic and clonic phases are largely influenced by subcortical facilitory actions on the lower motor neurons. Our studies demonstrate that associated changes obviously are not due to muscle hyperactivity, but suggest that they are central in origin.

SUMMARY

1. A technic for the study of seizure patterns is presented whereby muscle artifact in the electroencephalogram is eliminated. This procedure has limited but definite clinical usefulness in the electroencephalographic laboratory.

2. Additional evidence is presented indicating that alterations in cardiovascular status associated with seizure activity are central in origin.

3. Temporal dissociation of phenomena accompanying generalized seizures would not favor a simultaneous generalized neuronal excitability and exhaustion.

The authors wish to express grateful appreciation to Dr. Alexander T. Ross, chief of the department of neurology, Indiana University Medical Center, for his encouragement and support.

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■ Some modern physiologists are of opinion, that the immediate or proximate cause of epilepsy is a derangement of the organization of some part or parts of the brain and nerves within the cranium; and though this hypothesis is attended with several difficulties, it is by no means the least plausible that has been offered on the subject.

In epilepsy sensation is impeded, and motion is morbidly increased, and is no longer performed in obedience to the will. Now it is not unreasonable to suppose, that this may depend upon a deranged state of the organization of certain parts within the cranium, because we can have no doubt that whatever be the nature of the sentient, willing, and first moving power, it acts, and is acted upon, through the medium of organized matter; and, because on dissection after epilepsy, derangements of the organization of parts within the cranium have been very often actually found — In order that the perceiving power may act perfectly, it would seem that its instruments must be perfect. — For the perfection of vision, the organ of sight must be unimpaired. If the eye be obscured, sight will become obscure; if its transparency be restored, distinct vision will be restored. — Similar observations might be made respecting the other senses.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

PROGRAM OF THE
AMERICAN ACADEMY OF NEUROLOGY

Ninth Annual Meeting

April 22 – 27, 1957

Sheraton Plaza Hotel — *Boston, Massachusetts*

Review Courses in Basic and Clinical Neurology

April 22, 23, 24, 1957

Intensive review courses in basic and clinical neurology will be offered preceding the annual meeting, sponsored and arranged by the American Academy of Neurology. Courses will be held as follows:

Neuropathology—April 22, 1957

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Episodic Disorders of the Nervous System—April 23, 1957

Neurochemistry—April 23, 1957

The Brain and Its Communication Systems—April 23, 1957

Current Advances in Neurology—April 24, 1957

Neuropharmacology—April 24, 1957

Additional information regarding these courses may be obtained from Mrs. J. C. McKinley, Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota.

THURSDAY, APRIL 25, 1957

Morning Session *A* 9:00 a.m.

Chairman: Pearce Bailey, *Washington, D.C.*

Secretary: Elliott L. Mancell, *Boston, Massachusetts*

Junior Prize Essay
Subject and author to be anounced

Presidential Address

Walter O. Klingman, *Charlottesville, Virginia*

Common Sources of Error in the Diagnosis and Treatment of Convulsive Disorders

Robert B. Aird and Tadao Tsubaki, *San Francisco, California*

Neurogenic Pulmonary Edema

A. B. Baker, *Minneapolis, Minnesota*

Clinical Significance of Impairment of Sound Localization

Luis P. Sanchez Longo and Francis M. Forster, *Washington, D.C.*

Collateral Regeneration from Surviving Motor Nerve Fibers in Partially Denervated Muscles

Gunnar Wohlfart, *Lund, Sweden*

Clinical Aspects of the Integration of Movement

Derek Denny-Brown, *Boston, Massachusetts*

The Neuropathies of Diabetes

John F. Sullivan, *Boston, Massachusetts*

Collimation Detection of Brain Tumors with Zn^{65}, Zn^{69}, I^{131}, As^{74}

G. M. Shy, Robert Bradley, and William Matthews, *Bethesda, Maryland*

The Significance and Reliability of Various Signs and Symptoms in the Diagnosis of Level of Root Involved in Protrusion of a Cervical Disk

Robert E. Yoss, J. Grafton Love, Kendall B. Corbin, and Collin S. MacCarty, *Rochester, Minnesota*

THURSDAY, APRIL 25, 1957

Morning Session *B* 9:50 a.m.

Chairman: Charles Van Buskirk, *Baltimore, Maryland*

Secretary: Luis R. Lombardo, *Baltimore, Maryland*

A Study of Cholinesterases and Ali-esterase in Human Cerebrospinal Fluid in Various Neurologic Diseases

Joseph Bernsohn and Benjamin Boshes, *Chicago, Illinois*

A Study of Addiction to Non-ethyl Alcohols, and Other Poisonous Compounds

Jack Mendelson, Donald Wexler, P. Herbert Leiderman and Philip Solomon, *Brookline, Massachusetts*

Effect of Anticonvulsant Drugs in Animals with Chronic Focal Epileptogenic Lesions

Frank Morrell, William B. Bradley and Mark Ptashne, *Minneapolis, Minnesota*

Localizing Value of Oculocephalic and Caloric Responses in the Unconscious Patient

Morton Nathanson, Philip S. Bergman and Paul J. Anderson, *New York City*

Paralysis Following Seizures

Daniel Sciarra, *New York City*

Radioisotopic Studies of Nucleoprotein Metabolism in the Central Nervous System

Harold Koenig, *Chicago, Illinois*

Brain Vascularity and Localization of Radioactive Isoniazid by Autoradiography

Charles F. Barlow, J. C. Schooler and L. J. Roth, *Chicago, Illinois*

A Comparison Between Picrotoxin, Mikedimide, Electrical Stimulation and Physiological Support in Experimental Barbiturate Poisoning

Fred Plum and George S. Lavenson, *Seattle, Washington*

The Determination and Electrophoretic Fractionation of Serum and Cerebrospinal Fluid Proteins and Glycoproteins in Neurologic Diseases

Norman C. Hill, Bernard F. McKenzie, Warren F. McGuckin, Hendrik J. Svien and Norman P. Goldstein, *Rochester, Minnesota*

THURSDAY, APRIL 25, 1957

Afternoon Session 1:45 p.m.

Chairman: William F. Caveness, *New York City*

Secretary: C. Wesley Watson, *Boston, Massachusetts*

The Place of Mesantoin in the Treatment of Epilepsy: Efficacy vs. Toxicity

Harry L. Kozol, *Boston, Massachusetts*

Organization of Somatic Sensory and Motor Systems of the Cerebral Cortex

Clinton N. Woolsey, *Madison, Wisconsin*

Electrophysiological Analysis of Caudate-Cortical Relations (cat)

Dominick P. Purpura, Edgar M. Housepian and Harry Grundfest, *New York City*

The Long Lasting Effects of Reticular Formation Stimulation

Chandler McC. Brooks, Isamu Suda and Kiyomi Koizumi, *New York City*

Midbrain and Thalamic Evoked Responses in the Cat: Effects of Gaseous Anesthetic Agents and Muscle Relaxants

Clark T. Randt, William F. Collins, Hamilton S. Davis and William H. Dillon, *Cleveland, Ohio*

On the Abnormal Nature and Hereditary Character of Certain EEG Changes Evoked Experimentally by Flickering Light

C. Wesley Watson, Sherwood Davidson and Elliott Marcus, *Boston, Massachusetts*

Studies in Human Cerebral Function: The Vulnerability of Specific Features of the Highest Integrative Functions in Relation to the Loss of Increasing Amounts of Cerebral Hemisphere Tissue

Loring F. Chapman, William N. Thetford, Louis Berlin, Thomas C. Guthrie and Harold G. Wolff, *New York City*

The Mechanism of the Production of Papilledema in the Guillain-Barré Syndrome

R. J. Joynt, *Iowa City, Iowa*

Cerebellar Hemorrhage: A Clinicopathological Study

Jean Rey-Bellet, *New York City*

A Clinical Study of Aphasic Patients

Joe R. Brown and Josephine Simonson, *Rochester, Minnesota*

North American Blastomycosis of the Central Nervous System: A Clinico-Neuropathological Review of 12 Cases

Kathryn R. Lewis and William W. Ayres, *Washington, D.C.*

Business Meeting 5:00 p.m.

Walter O. Klingman, presiding

THURSDAY, APRIL 25, 1957

Evening Session 8:00 p.m.

A SYMPOSIUM OF INQUIRY

What We Need to Know About Muscle

This is a prepared two-hour discussion by four eminent scientists, designed to summarize knowledge of muscle and to emphasize the areas where more research is needed. Written questions from the floor will be encouraged and answered by the panel. Speakers will be:

G. Stanley Bennett—Morphology
Albert Szent-Gyorgyi—Biochemistry
Derek Denny-Brown—Physiology
Raymond D. Adams—Pathology

This is the third symposium of inquiry sponsored by the research committee of the Amer-

ican Academy of Neurology. It is intended to stimulate thinking and provoke research ideas. The proceedings will be transcribed and subsequently published.

FRIDAY, APRIL 26, 1957

Morning Session *A* 9:00 a.m.

Chairman: Donald B. Tower, *Bethesda, Maryland*

Secretary: Maynard M. Cohen, *Minneapolis, Minnesota*

COLLOQUIUM ON NEUROCHEMISTRY

The Development of Neurochemistry
Donald B. Tower, *Bethesda, Maryland*

Maintainance of the Composition of Isolated Cerebral Tissues
Henry McIlwain, *London, England*

Metabolism of Nucleic Acids and Lipides in Brain and in Peripheral Nerve During Experimental Demyelination
R. J. Rossiter, *London, Canada*

A Specific Antidote for Nerve Gas and Insecticide (Alkylphosphate) Intoxication
Irwin B. Wilson, *New York City*

FRIDAY, APRIL 26, 1957

Morning Session *B* 9:00 a.m.

Chairman: J. Preston Robb, *Montreal, Quebec*

Secretary: William Tatlow, *Montreal, Quebec*

Familial Acute Infantile Cerebral Degeneration
Paul M. Ellwood, Jr., Frank Morrell and Erland Nelson, *Minneapolis, Minnesota*

Behavior of Reserpinized Chimpanzees
Jane Joralemon and W. F. Windle, *Bethesda, Maryland*

Pathogenesis of Hypophyseal Duct Tumors
O. Hirsch and H. Hamlin, *Providence, Rhode Island*

The Variability of Untreated Phenylketonuria
Richmond S. Paine, *Boston, Massachusetts*

Studies in Myasthenia Gravis
Kermit E. Osserman, *New York City*

The Nature of Defective Grasping in Infantile Spastic Hemiparesis
Thomas E. Twitchell, *Boston, Massachusetts*

Cerebellar Ataxia, Progressive External Ophthalmoplegia and Cataracts
Luis R. Lombardo, *Baltimore, Maryland*

Myasthenia Gravis Appearing After Removal of Thymoma
Lewis P. Rowland, Henry Aranow, Jr., and Paul F. A. Hoefer, *New York City*

Post-Irradiation Cervical Myelopathy
Hideo H. Itabashia, Jose Bebin and Russell N. DeJong, *Ann Arbor, Michigan*

Spinal Hemangiomas in Pregnancy
William S. Fields, *Houston, Texas*

The Clinical Significance of the Myelographic Defect
Paul J. Anderson, *New York City*

Tuberculoid Leprosy: A Report of Two Cases
Thomas B. Summers and George R. Zimmerman, *Iowa City, Iowa*

FRIDAY, APRIL 26, 1957

Afternoon Session 1:45 p.m.

Chairman: Gilbert H. Glaser, *New Haven, Connecticut*

Secretary: Paul S. Slosberg, *New York City*

The Central Nervous System in Congenital Heart Disease
Maynard M. Cohen and A. B. Baker, *Minneapolis, Minnesota*

Higher Brain Functions and Differential Aging
Ward C. Halstead, *Chicago, Illinois*

Serum Glutamic Oxalacetic Transaminase in Neurologic Disease
Robert G. Siekert and Gerard A. Fleisher, *Rochester, Minnesota*

Architecture of the Optic Radiation in the Temporal Lobe
John M. Van Buren, *Bethesda, Maryland*

Micro-determination of Protein and Lipides in CSF
Wallace W. Tourtellotte and Russell N. DeJong, *Ann Arbor, Michigan*

A Review of Cerebral Hemispheric Tumors with Attention to Presence or Absence of Extrapyramidal Signs and Symptoms
R. Roth and J. Bebin, *Detroit, Michigan*

Some Relationships Between Interictal Spiking Foci and Ictal Seizure Discharges
Bruce L. Ralston, *Bethesda, Maryland and New York City*

Familial Dysautonomia
Webb Haymaker and Harold Stevens, *Washington, D.C.*

Effects of Brainstem Lesions in Monkeys on Optokinetic Nystagmus

P. Teng, S. Shanzer and M. B. Bender, *New York City*

Transient Epileptogenic Encephalopathy in Children

Ralph Druckman, Dora Chao and Peter Kellaway, *Houston, Texas*

Glutamic-Oxaloacetic Transaminase Activity in Spinal Fluid

Robert Katzman, Robert A. Fishman and Eli S. Goldensohn, *New York City*

Understanding Oscillations in Normal and Diseased Neurological Servomechanisms

Lawrence Stark, *New Haven, Connecticut*

Business Meeting 5:00 p.m.

Walter O. Klingman, presiding

SATURDAY, APRIL 27, 1957

Morning Session 9:00 a.m.

Chairman: Sidney Carter, *New York City*

Secretary: Eugene Loeser, *New York City*

Benign Intracranial Tumors of Childhood

Donald D. Matson, *Boston, Massachusetts*

Polyneuritis in Children

Niels L. Low, *Salt Lake City, Utah*
Julia Schneider and Sidney Carter, *New York City*

Brainstem Tumors in Children

Patrick F. Bray, *Salt Lake City, Utah*
Sidney Carter and Juan Taveras, *New York City*

Neurological Abnormalities in Infants Born to Diabetic Mothers

A. S. Dekaban and K. Magee, *Bethesda, Maryland*

Subdural Hematoma and Subarachnoid Hemorrhage Among Infants and Children: Review of 50 Cases

Robert W. Hollenhorst, Harold A. Stein, Haddow M. Keith and Collin S. MacCarty, *Rochester, Minnesota*

Anticoagulant Therapy in Cerebral Thrombosis

C. M. Fisher, *Boston, Massachusetts*

Basilar Artery Thrombosis: A Clinical and Pathological Study

Huberto Cravioto, Jean Rey-Bellet, Philip Prose and Irwin Feigin, *New York City*

Arteriographic Demonstration of Collateral Cerebral Circulation in Occlusive Cerebrovascular Disease

Gerard M. Lehrer, *New York City*

The Neurological Complications of Hodgkin's Disease

Joseph G. Chusid and C. G. De Gutiérrez-Mahoney, *New York City*

Cerebral Pathology Found in Fatal Rupture of Cerebral Artery Aneurysms

Sherwood A. Jacobson, *New York City*

Evaluation of Mental and Emotional Changes in Epileptics on Continuous Anticonvulsant Therapy

Nathene Loveland, Bushnell Smith and Francis Forster, *Washington, D.C.*

SATURDAY, APRIL 27, 1957

Afternoon Session 12:45 p.m.

Chairman: Irwin Levy, *St. Louis, Missouri*

Secretary: Edward F. Vastola, *New York City*

Oculomotor and Postural Patterns in Schizophrenic Children

Max Pollack and Howard P. Krieger, *New York City*

Electroencephalographic Evaluation of Therapy in Obstructive Disease of the Basilar and Carotid Arteries

J. S. Meyer, W. Wegner, C. A. Kane and O. Reinmuth, *Boston, Massachusetts*

The Treatment of Cryptococcosis: A Review with Report of a Case

G. W. Holt, W. C. Robb, K. C. Sawyer and J. List, *Denver, Colorado*

Neurological Significance of Gerstmann's Syndrome

Robert F. Heimburger, William DeMyer and Ralph M. Reitan, *Indianapolis, Indiana*

Psychological Significance of Gerstmann's Syndrome

Ralph M. Reitan, William DeMeyer and Robert F. Heimburger, *Indianapolis, Indiana*

Lesions of the Basal Ganglia of the Monkey

George D. Davis, *New Orleans, Louisiana*

Restoration of Function in Aphasia: A Survey of Three Years' Experience in a Rehabilitation Setting

Morton Marks, Martha Taylor and Howard A. Rusk, *New York City*

Uremia, Coma and the EEG

Jerome Kassirer, Walter Stafford and Irving Hyman, *Buffalo, New York*

Clinical and Physiologic Studies of Normal Sleep and Narcolepsy

R. I. Birchfield, H. O. Sieker and A. Heyman, *Durham, North Carolina*

Peripheral Neuropathy Associated with Hereditary Primary Systemic Amyloidosis

Joshua H. Carey, Charles E. Jackson, Harold F. Falls, John G. Rukavina and Walter D. Block, *Ann Arbor, Michigan*

Subacute Inclusion Encephalitis

Richard G. Berry, Harold M. Manfredi and Bernard J. Alpers, *Philadelphia, Pennsylvania*

Familial Areflexic Amyotrophy: A Genetic Form of Myeloneuropathy

I. S. Freiman, *New York City*

Distribution of Radioarsenic in Normal Tissues and Intracranial Neoplasm in Man

G. L. Brownell, W. H. Sweet and J. Mealey, *Boston, Massachusetts*

AMERICAN ACADEMY OF NEUROLOGY

SECTION ON NEUROCHEMISTRY

THURSDAY, APRIL 25, 1957

Afternoon Session 1:30 p.m.

Chairman: Roscoe O. Brady, *Bethesda, Maryland*

Secretary: Robert M. Burton, *Bethesda, Maryland*

Some Aspects of the Relation of Ceruloplasmin to Wilson's Disease

I. Herbert Scheinberg, Ruth S. Harris and Donald Dubin, *New York City*

Muscle Proteins in Dystrophy

Bennie Horvath, *Bethesda, Maryland*

A Collagen-like Compound Isolated from Spinal Cord

Elizabeth Roboz, Nezahat Henderson and Marian W. Kies, *Washington, D. C.*

Nucleic Acid Content of Cerebral Neurons

R. G. Grenell and Leopold May, *Baltimore, Maryland*

Quantitative Histochemistry of Selected Central Tracts

D. B. McDougal, Jr., *St. Louis, Missouri*

Substrate Utilization of Peripheral Nerves

Irving H. Heller and Sigurd Hesse, *Montreal, Quebec*

Increase in the Rate of Glucose Utilization During Activity in Excised Sympathetic Ganglia

Michel Dolivo and Martin G. Larrabee, *Baltimore, Maryland*

Effect of Glutamate and Glutamine on the Intracellular Electrolytes of Nervous Tissues

Adelbert Ames, *Boston, Massachusetts*

Diffusion Constants in the Extracellular Space of Brain Tissue

Hugh McLennan, *Halifax, Novia Scotia*

Mitochondria of Brain as the Site of its Metabolic Activity

H. G. deBuy, *Bethesda, Maryland*

Business Meeting (Organization session) 5:10 p.m.

FRIDAY, APRIL 26, 1957

Joint meeting with general session 9:00 a.m.

COLLOQUIUM ON NEUROCHEMISTRY

FRIDAY, APRIL 26, 1957

Afternoon Session 1:30 p.m.

Chairman: William K. Jordan, *Little Rock, Arkansas*

Secretary: Irving H. Heller, *Montreal, Quebec*

The Adenosine Polyphosphates, Creatine Phosphate and Ascorbic Acid Content of Rat Brain

Sping Lin, Harold P. Cohen and Maynard M. Cohen, *Minneapolis, Minnesota*

Some Aspects of Oxidative Metabolism of Glucose in Brain Suspensions

Malcolm Gordon, Peter Hawley and M. K. Gaitonde, *Hartford, Connecticut*

Metabolic Studies of Gamma-Aminobutyric Acid

Eugene Roberts and Claude Baxter, *Duarte, California*

Studies with Tritium-Labelled Inositol

Bernard W. Agranoff and Roscoe O. Brady, *Bethesda, Maryland*

Studies on the Biosynthesis of Cerebroside Galactose

Hugo W. Moser and Manfred L. Karnovsky, *Boston, Massachusetts*

Studies on the Biosynthesis of Galactolipids

Robert M. Burton, Mary H. Sodd and Roscoe O. Brady, *Bethesda, Maryland*

A Comparison of the Biochemistry of Wallerian Degeneration in the Peripheral and Central Nervous Systems

Richard E. McCaman and Eli Robins, *St. Louis, Missouri*

Studies on Myelination and Demyelination: Lipogenesis by Nervous Tissue In Vitro

Guido Manjo and Manfred L. Karnovsky, *Boston, Massachusetts*

Mode of Action of an Inhibitor of Acetylcholine Synthesis

F. C. McIntosh, R. I. Birks and P. B. Sastry, *Montreal, Quebec*

Correlation of Rate of Compulsive Circling in Rabbits with Asymmetric Accumulation of Acetylcholine in their Cerebral Cortices

M. H. Aprison, *Indianapolis, Indiana*

SATURDAY, APRIL 27, 1957

Morning Session 9:00 a.m.

Chairman: Maynard M. Cohen, *Minneapolis, Minnesota*

Secretary: John Logothetis, *Minneapolis, Minnesota*

Butyrylcholinesterase in Human and Ruminant Nervous Tissue

Joseph Bernsohn and Leroy Possley, *Chicago, Illinois*

The Effect of Prolonged Treatment with Tranquilizing Drugs upon Two Enzymes of the Central Nervous System

Winifred Ashby, *Washington, D. C.*

Evidence for Action of Tranquilizing and Hallucinogenic Drugs by Central Interaction with Serotonin and Norepinephrine

Donald Bogdanski, Sydney Spector, Parkhurst A. Shore and Bernard B. Brodie, *Bethesda, Maryland*

Factor I and Gamma-Aminobutyric Acid

K. A. C. Elliott, *Montreal, Quebec*

Cerebral Blood Flow in Epileptic Children During the Interseizure Period

Charles Kennedy, William Anderson and Louis Sokoloff, *Philadelphia, Pennsylvania*

The N-methylated Derivatives of Barbituric Acid, Hydantoin and Oxazolidinedione Used in the Treatment of Epilepsy

Thomas C. Butler and William J. Waddell, *Chapel Hill, North Carolina*

Relation Between Excitability and Metabolism in Brain as Elucidated by Anticonvulsant Drugs

Dixon M. Woodbury and Alan R. Koch, *Salt Lake City, Utah*

Sound-Induced Seizures in Animals

Cary Suter, Walter O. Klingman, Dane Boggs, R. D. Marks, Carl B. Caplinger and O. W. Lacy, *Charlottesville, Virginia*

The Composition of Cerebrospinal Fluid under Varying Conditions

Edgar A. Bering, *Boston, Massachusetts*

Biochemical Changes in Brain and Spinal Fluid after Head Injury

Ernest Sachs, Jr., John Davison, Lucia Phillips, Fred Chang and James Ryan, *Hanover, New Hampshire*

CASE REPORT

Intracranial Venous Thrombosis During the First Trimester of Pregnancy

Robert A. Fishman, M.D., David Cowen, M.D. and Maximilian Silbermann, M.D.

THROMBOSIS of the dural venous sinuses and veins is most frequently a complication of infection in the paranasal sinuses or mastoids.[1] However, cranial injury may on rare occasion predispose to thrombus formation without evidence of sepsis.[2] The "marantic" illnesses, such as leukemia, tuberculosis, persistent diarrhea, and other diseases associated with severe dehydration, have in the past been associated with the occurrence of aseptic thrombosis of the dural sinuses.[3] The occurrence of aseptic dural sinus thrombosis has been described also as an uncommon complication of the postpartum period, usually occurring within three weeks after delivery.[1,4–6] Thrombosis of the superior longitudinal sinus has been reported as a spontaneous occurrence, in the absence of sepsis, trauma, marasmus, or the puerperium, and such cases have been considered primary thrombosis of the dural sinuses.[7] The clinical picture in such cases is variable and may include focal neurologic signs, with or without increased intracranial pressure, convulsions, subarachnoid hemorrhage, and the syndrome of pseudotumor cerebri.

The spontaneous occurrence of thrombosis of the superior longitudinal sinus in two patients during the third month of pregnancy has prompted the report of this unusual syndrome.

Case 1. A 20 year old woman in her third month of pregnancy was in good health until one week prior to admission when she complained of easy fatigability. There were no specific complaints until the day of admission when she became confused and began to scream incoherently. The local physician was called and he informed the family that she had a "nervous breakdown." A short time later she became progressively more stuporous and was admitted to the Neurological Institute in a comatose state. The past history was not significant.

On admission the patient was deeply comatose. There was stiffness of the neck and bilateral Kernig and Brudzinski's signs were observed. The temperature was 99° F., pulse 110, respirations 28 and blood pressure 140/90. Physical examination was not otherwise remarkable, except for a few rales at the lung bases and labored respirations. Neurologic examination revealed no lateralizing signs. The fundi were normal, the reflexes were hypoactive bilaterally, and there were bilateral extensor plantar responses. Lumbar puncture was performed shortly after admission. The pressure was increased, but at this time the patient was convulsing. The fluid was initially clear, but then became grossly bloody. It was believed at the time that the blood probably was due to trauma at the puncture site. Urinalysis was

From the departments of neurology and neuropathology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, Presbyterian Hospital, New York City.

not remarkable. Blood and spinal fluid serologic tests for syphilis were negative. No additional laboratory data were obtained prior to death.

Shortly after admission she began to have episodical attacks characterized by rhythmic clonic contractions of the upper and rigidity of the lower extremities. The movements gradually became more severe and within one-half hour a generalized tonic convulsion occurred, lasting about one minute, which appeared to be more severe on the left side of the body. Following the seizure the involuntary movements ceased and the signs of meningeal irritation and the extensor plantar responses disappeared. One hour later, six hours after hospital admission, the patient's respiration suddenly ceased and she was pronounced dead. No definite clinical diagnosis was made, but an acute meningoencephalitis was considered possible.

Postmortem examination. The superior longitudinal sinus was filled with a firm thrombus which completely occluded the torcular Herophili. The thrombus extended into both lateral sinuses, more so on the left than the right. The blood vessels of the brain were enormously congested, particularly the veins over the dorsal portions of the hemispheres. On section, there were small miliary hemorrhages throughout the cortical grey matter, especially in areas adjacent to the thrombosed sinuses. There were no gross lesions in the white matter, basal ganglia, brainstem, and cerebellum. The petrous bone, the middle ear, and mastoid cells were normal. The frontal, ethmoid, and sphenoid sinuses were also normal. The lungs were not remarkable, except for the presence of several pulmonary emboli. No source for emboli other than the dural thrombus was noted. The heart was normal. The gross findings at autopsy were otherwise negative, except for the uterus which was enlarged to the size expected at the end of the first trimester of pregnancy. There was no evidence of any focus of infection. *Staphylococcus albus* was cultured from the central nervous system at necropsy but this was considered to be a contaminant. On microscopic examination, the walls of the dural sinuses contained numerous small areas of hemorrhage but there was no evidence of infection. There was thrombus formation with attachment to the dural wall, suggesting early organization. The brain was intensely congested, the pial veins were thrombosed, and there were many small miliary hemorrhages in the cortical grey matter and small areas of encephalomalacia. There were small areas of subependymal hemorrhage in the walls of the lateral ventricles. There was no evidence of an inflammatory or glial reaction.

Case 2. A 27 year old woman in her third month of pregnancy was in excellent health until seven days prior to admission. At this time she had a slightly bloody vaginal discharge and was confined to her home by order of her physician. She was given stilbestrol 25 mg. six times daily for four days. She vomited on several occasions, complained of weakness, and spent most of the day in bed. She was afebrile. Three days prior to admission the husband noted that the patient staggered and tended to walk to the left on arising from bed. She also complained of generalized headache, and of not seeing clearly on looking to the left. Two days prior to admission she was noted to be confused, failing to remember that she had eaten breakfast. She became drowsy in the afternoon and was disoriented as to time and place. That evening she had a convulsion, described as beginning with the head and eyes turned to the right, with twitching in the right extremities which progressed to a generalized convulsion. She remained comatose postictally and was admitted to a community hospital. The day prior to transfer to the Neurological Institute she remained comatose and was reported to have had repeated generalized convulsions. That evening she was described as in deep coma, without nuchal rigidity. The pupils were fixed to light and equal. Bilateral convulsive movements were described, followed by increased tone on the left side. The deep tendon reflexes were more active on the left side and there was a positive Babinski sign on the left.

She was transferred to the Neurological Institute at 12:30 a.m. At this time the blood pressure was 130/70, pulse 100, respirations 24, and temperature 99.6°F. She responded only to painful stimuli by withdrawal of the stimulated extremity, with more activity of the right than the left side. There was increased tone in all the extremities, more marked on the left. There was a generalized and symmetric increase in reflex activity, with bilateral extensor plantar responses. The pupils were unequal (right 2 mm., left 4 mm.), the right reacting sluggishly to light and the left being fixed. There was a weak consensual reaction on stimulation of the right eye. There was deviation of the head and eyes to the left. There was blurring of the margins of the optic disks bilaterally but no other abnormal findings. Physical examination was otherwise not remarkable. Emergency skull films taken on admission were reported to be normal.

One hour after admission the coma deepened and the patient became completely unresponsive. The extremities were flaccid and no reflexes could be obtained. Both pupils were

equal and fixed. Periods of apnea lasting almost a minute then developed. Oxygen and artificial respiration were administered. Caffeine and adrenalin were also given. At this point the blood pressure was 134/64, temperature 102, and pulse 160. The cardiac rhythm was irregular. The patient was placed in a respirator, but the heart failed one hour later. No other laboratory studies could be obtained during the two and one-half hour period that the patient survived at the hospital.

No definite clinical diagnosis was made. The possibility of a dural sinus thrombosis was considered, in view of the similarity to the course of the previous case described.

Postmortem examination. The superior longitudinal sinus was filled with a massive pinkish-brown thrombus extending for 10 cm. from a point 2 cm. posterior to the attachment of the sinus at the crista galli to about 1 cm. anterior to the torcular Herophili. This friable thrombus had extended into some of the superior cerebral veins. The dura and the other venous sinuses were not unusual. No evidence of infection was found in the mastoid or in the ethmoid, frontal, and sphenoid sinuses. The cerebral hemispheres were asymmetric due to the presence of an extensive recent subarachnoid hemorrhage over the right frontal area. The underlying cerebral tissue was soft and friable. There was a smaller area of leptomeningeal hemorrhage over the left frontal area. The superior cerebral veins leading toward the thrombosed sinus were distended due to thrombosis. This was most marked in the left frontal region. The remainder of the leptomeninges over the convex surface of the hemispheres, as well as those at the base, were not remarkable. The arteries of the brain were normal. There were tentorial grooves on the ventral aspect of each uncus. The cerebellum and brainstem were normal externally. Many recent hemorrhages in the cortex and white matter of the hemispheres were seen in transverse sections of the brain. These were largest in the areas adjacent to the leptomeningeal clots, but were widespread throughout each hemisphere. There were also many satellite hemorrhages and some petechial lesions. There was an area of hemorrhage in the right parietal lobe communicating with the right lateral ventricle which was filled with clot. Cultures taken from the sinus and brain were sterile. No other thrombi were noted. There was a normal three month old fetus in utero. Otherwise, there were no significant abnormalities in the necropsy.

On microscopic examination the superior sagittal sinus was filled with laminated recent thrombus material. There was no evidence of inflammation in the walls of the sinuses or in the blood vessels. There was hemorrhagic infarction of the cerebral tissue and thrombosis of the veins in the areas which appeared abnormal on gross examination. All of the cerebral lesions were acute and of about the same duration. There were no changes suggestive of previous episodes of thrombosis.

DISCUSSION

These two patients present a very striking clinical situation in which previously healthy women in the third month of an uncomplicated pregnancy developed an acute organic mental state, followed by rapidly progressive stupor associated with focal and generalized convulsions. Both ran a rapidly fatal course, terminating with deep coma with respiratory arrest. The similarity of the illness of the second patient to that of the first was such that the diagnosis was suggested shortly before death. In neither case could the cause for thrombus formation in the superior longitudinal sinus be determined. There was no evidence of thrombus formation in other areas of the body, nor was there any evidence of infection in the paranasal sinuses or the meninges. There was no evidence of trauma or debilitating disease. Death occurred so rapidly that hematologic studies could not be performed to determine the presence or absence of a derangement of the blood clotting mechanism.

The relationship of pregnancy to thrombus formation in the dural sinuses is obscure. This syndrome has been described as occurring from two to 28 days after delivery, but not as a complication of the first trimester.[1,4–6] The etiology of postpartum thrombus formation remains unexplained, although changes in the circulation of the deep paravertebral venous plexus occurring during labor have been suggested as having a role in the formation of a thrombus in the intracranial venous sinuses.[5] The possibility of a rent in the intima of the dural sinuses occurring during labor, associated with the usual postpartum increase of blood platelets and plasma fibrinogen, has been suggested as a basis for

thrombus formation.[1] It would be difficult to relate such processes to thrombosis in the first trimester of pregnancy.

In view of the similarity of the course of these two patients, it may be possible that an early diagnosis could be made in such cases. The possibility of therapy would appear limited, especially in patients with evidence of extensive hemorrhagic infarction. Spontaneous recovery has been reported in patients with postpartum thrombosis of the dural sinuses,[6] but catastrophic hemorrhagic infarction did not occur in these cases. Administration of anticoagulants might be considered as rational therapy.[8] This would be hazardous if there were evidence of extensive intracerebral or subarachnoid bleeding, but could be considered in less fulminant and massive occlusions. In view of the extension of the thrombus into the cortical veins, the value of thrombectomy would be limited.

SUMMARY

Two patients are reported who developed a spontaneous thrombosis of the superior longitudinal sinus during the first trimester of pregnancy. The clinical picture associated with this lesion was characterized by the acute onset of an organic mental syndrome, followed by generalized convulsions, progressive stupor, and death from respiratory arrest within a few days of the onset. At necropsy there was hemorrhagic infarction of the cerebral cortex, secondary to aseptic thrombosis of the superior longitudinal sinus. No cause for the thrombus formation could be determined.

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6. Hyland, H. H.: Intracranial venous thrombosis in the puerperium. J.A.M.A. 142:707, 1950.
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Neurology

BOOK REVIEWS

Epilepsy and the Law

Roscoe L. Barrow and Howard D. Fabing, M.D. 1956. New York: Paul B. Hoeber, Inc. 177 pages. $5.50.

DEAN Roscoe L. Barrow of the University of Cincinnati College of Law and Dr. Howard D. Fabing, past president of the American Academy of Neurology and chairman of the legislation committee of the American League against Epilepsy, have collaborated in a detailed study of the legal aspects of epilepsy. The publication of this book marks an important monument in the attack on this important disease, and it is the first major document to clarify the legal and social status of the epileptic patient in this country. It provides a firm, factual basis on which to formulate corrective action for certain of the inequities that make the epileptic's position in society so insecure.

Four major aspects of legal restrictions of the epileptic are investigated in detail. These include studies on marriage license laws, sterilization laws, driver's license laws, and workmen's compensation laws. It is brought out that, not only is there a great deal of inconsistency in these laws in the various states of our country, but also the majority of them are outmoded and based on concepts of epilepsy which have long been disproved in view of recent research and knowledge. It is a well documented, objective appraisal of individual state laws governing the epileptic's ability to marry and have children, to drive a motor vehicle, and to obtain employment, and specific recommendations are made in regard to each of these. Most of the laws are based on the stigma that has been attached to epilepsy since prehistoric times, and this stigma is a formidable obstacle to social rehabilitation. Furthermore, in the majority of laws there is no definition of "epilepsy," and in many states epilepsy is included in a general way with idiocy and insanity.

Medical progress in the control of epileptic seizures has rendered our epilepsy laws anachronistic. In this book, proposals are made for legislative changes that will bring these laws into line with modern medical knowledge of this disease. Such changes are necessary if the legal aspects of epilepsy are to keep pace with the medical gains that have been made in recent years in the treatment of this condition.

R. N. DE J.

Examination of the Nervous System

A Student's Guide. A. Theodore Steegmann. 1956. Chicago, Illinois: The Year Book Publishers, Inc., 164 pages. $3.75.

THIS small compendium on the technic of the neurologic examination is well planned and well executed to serve its announced purpose: that of a guide for medical students to the rudiments of the examination of the nervous system. The book contains what the average medical student should be expected to know about the subject. The outline used follows a conventional plan, and contains enough textual exposition of method and of relevant neuroanatomy and neurophysiology to make the presentation clear and meaningful. There are also a number of useful line drawings. There is a commendable avoidance of pointless eponyms. The book is inexpensive and small enough to fit the student's pocket—further points to recommend it to teachers of neurology and physical diagnosis.

R.B.R.

Editorial Note

MODES OF INHERITANCE AND GENETIC COUNSELLING

One of the ultimate objectives of any investigation in medical genetics is "prediction." The question the genetic counsellor must answer may take one of several forms. The parents of an affected child may ask: "If we have another child, what are the chances that it too will be affected?" or an affected individual may ask: "If I marry, what are the chances that my children will be affected?"

In so far as a sound "prediction" to these and other similar questions depends upon a sound "recognition" of the mode of inheritance, the authors of the interesting article "Familial Cerebello-Olivary Degeneration with Late Development of Rigidity and Dementia" (Neurology 6:876, 1956) have erred in their conclusion that "the defective genes in this pathologic condition of the nervous system are sex-linked recessive ones." The pedigree clearly suggests that the condition is due to a single autosomal dominant gene.

The difference that this makes in genetic counselling is too great to be ignored. For example, if the condition were due to a sex-linked recessive gene, the three living affected brothers (P.E.R., S.I.L., and L.A.W.) would not have affected children. However, the condition being due to an autosomal dominant gene, one must counsel that 50 per cent of their children, whether male or female, will be affected.

JULIUS D. METRAKOS, Ph.D.
Department of Medical Genetics,
The Montreal Children's Hospital

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1. Millichap, J. G., and Hedra, R.: Quantitative Assessment of Motor Function in Cerebral Palsy: Evaluation of Zoxazolamine (Flexin), A New Muscular Relaxant Drug, Neurology 6:843, 1956.

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MARCH 1957

AAN Program Expanded to Meet Rising Activities in Neurology As of the deadline (Jan. 11) for abstracts of papers to be presented in the scientific sessions of the coming AAN meeting at the Sheraton-Plaza Hotel in Boston (April 25-27), 160 high quality abstracts had been submitted to Program Chairman James L. O'Leary. Contrasted to the average 40 abstracts received for previous annual meetings, this sudden avalanche posed a last minute decision to be made by President Klingman, Program Chairman O'Leary, and Local Chairman Joseph M. Foley. The problem has been resolved by streamlining the program by having concurrently running scientific sessions, and by adding an afternoon of scientific sessions on Saturday (April 27). Thus, the scientific sessions will comprise 112 papers, including 30 papers to be presented by the AAN Section on Neurochemistry. In addition, there will be a Symposium of Inquiry on Muscle (see Newsletter, January 1957), which will take place at the Jimmy Fund Building Auditorium in the Children's Medical Center, Thursday evening (April 25). According to Program Chairman James L. O'Leary, "This will be the biggest and most exciting program we ever have had in American neurology -- or, at least, so I believe it to be."

Calendar of Social Events Tentatively arranged for the AAN meeting at the Sheraton-Plaza is the traditional Early Bird Party to be held at 5:30 p.m. on Wednesday (April 24) in the hotel foyer. The official banquet and dance is scheduled for Friday evening (April 26), and will be preceded by cocktails at 7 o'clock. Also, tentatively arranged, with the cooperation of the Woman's Auxiliary, are a Thursday afternoon visit to the Gardner Museum with a tour of the Palace, and an opportunity to attend, the same evening, the rehearsal of the Boston Symphony Orchestra. Plans are in the making for guided tours of the Museum of Fine Arts, the Museum of Science, and other landmarks of historic Boston on Friday afternoon. Data on restaurants and points of historic interest are being prepared.

New Honorary Members Elected to AAN AAN President Walter O. Klingman announces that the following distinguished neurologists and scientists have been elected as honorary members to the AAN: James B. Ayer, Alexander Forbes,

Stanley Cobb, and Wilder Penfield.... Recently elected to honorary-corresponding membership are Sir Henry Dale of London and Prof. Dr W. R. Hess of Zurich, Nobel laureates in 1936 and 1949, respectively.... There are now 11 honorary members and 49 honorary-corresponding members in the Academy.

* * * * * *

New Diplomates in Neurology At the annual examination of the American Board of Psychiatry and Neurology held in New York City (Dec. 10-11), 14 candidates were certified in neurology: James Henry Austin, Portland, Ore.; Robert E. Cook, San Francisco; Donald B. Douglas, New York City (supplementary certification); Bruce Carlyle, Peoria, Ill.; Norman Philip Goldstein, Rochester, Minn. (supplementary certification); Warren H. Kempinsky, St. Louis; Martin M. Mandel, Philadelphia; John Moossy, New Orleans; Thomas C. Parsons, Montrose, N. Y.; William Austin Sibley, Cleveland; Stanley A. Skillicorn, San Jose, Calif.; Janice Robinson Stevens, Portland, Ore.; Robert L. Tentler, Chicago; and Howard Jerome Tucker, New York City.... Two examinations will be given in 1957: New Orleans, Louisiana (March 18-19); New York, N. Y. (December 16-17).... The secretary-treasurer of the board announces that "Effective January 1, 1958, all unused examination fees, or portion thereof, on deposit in the Board Office will be forfeited by the candidate to the Board when the application lapses by going out of date. Further, all unused examination fees, or partial, unused examination fees, deposited before the date of January 1, 1952, will automatically be forfeited by the candidate to the Board on January 1, 1958."... Inquiries and communications should be directed to David A. Boyd, Jr., Secretary-Treasurer, American Board of Psychiatry and Neurology, 102-110 Second Ave. S.W., Rochester, Minn.

ANA to Meet in Atlantic City The 82nd annual meeting of the American Neurological Association will be held at the Claridge Hotel in Atlantic City (June 17-19). The scientific sessions begin on Monday morning, June 17, and continue through Wednesday morning, June 19. The annual dinner is scheduled for Tuesday evening, June 18. Members applying for a place on the program should submit an abstract in duplicate, not to exceed 200 words, to the secretary before March 15, and a resume, not to exceed 1,000 words, for publication in the Transactions. Nonmembers may read papers of special interest by invitation of the program committee. Presentations will be limited to 10 minutes. Those submitting papers should indicate to the secretary the name of one or two discussants. Applications for exhibits and demonstrations are encouraged.... All communications should be sent to Dr. Charles Rupp, 133 South 36th Street, Philadelphia 4, Pa.

Symposium on Myelin To Precede ANA Meeting

On Saturday and Sunday, June 15-16, just before the ANA meeting, there will be a symposium on myelin at the Claridge Hotel, Atlantic City. According to the symposium chairman, Saul R. Korey, professor of neurology, Albert Einstein College of Medicine, Yeshiva University, the problem will be approached in all its biologic aspects and constitute a comprehensive analysis of the constituents of myelin and of the known structural and dynamic factors in the myelinization process.

Division of Neurology Established at Western Reserve

A division of neurology has been established at Western Reserve University Medical Center in Cleveland. Director of the division is Clark T. Randt, who will be assisted in developing a three-year residency training program in neurology by William A. Sibley, Lowell H. Lapham, Howard J. Tucker, John H. Nichols, and Robert F. Bennett. The program will emphasize neurologic training in its clinical and basic aspects.

* * * * * *

Random Notes On International Congress

The registration deadline for the First International Congress of Neurological Sciences in Brussels is April 1, 1957. After this date the registration fees (active, $15.00; associate, $10.00; auxiliary, 5.00) are doubled. Registration fees are not refundable. Titles and abstracts of presentations for the scientific sessions will not be included in the printed program unless the author has registered.... The official reception for members of the congress will be given Sunday evening, July 21. Subscriptions ($9.00 per person) to the official banquet and dance set for Thursday evening, July 25, must be paid before March 20.... An historic exhibit, designed by Secretary-General Ludo van Bogaert, which features Vesalius and the history of anatomy, will be unveiled on Monday, July 22.... The House of Travel (17 East 49 Street, New York 17, N. Y.) offers escorted grand tours of Europe for neurologists and scientists, which include attendance at the Brussels congress.... Additional details about the congress may be obtained from Dr. Pearce Bailey, Secretary, Committee for the United States, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.

Other International Congresses Related to Neurology

Other international congresses in disciplines related to neurology which will be held in Western Europe this summer are: Fourth International Poliomyelitis Congress in Geneva (July 8-12); Anglo-American Conference on "The History of Knowledge of the Functions of the Brain" in London (July 15-18); a Symposium on the "Medical-Social Aspects of Senile Nervous Diseases" to be held under the auspices of the Fourth Congress

of the International Association of Gerontology in Venice (July 20-21); the Fifteenth International Congress of Psychology in Brussels (July 28-August 3); and the International Congress of Psychiatry in Zurich (September 1-7).

Princeton Conference On Cerebral Vascular Disease Under the sponsorship of the American Heart Association, aided by grants from the National Heart Institute and the Albert and Mary Lasker Foundation, the Second Conference on Cerebral Vascular Diseases was held at Princeton's Nassau Tavern (Jan. 16-19). A program committee, composed of Irving S. Wright, chairman; Clark Millikan, vice-chairman and editor; E. Cowles Andrus, and Miller Fisher, opened the sessions Wednesday evening (Jan. 16) with a discussion of the problem of nomenclature and classification of cerebral vascular disease (Clark Millikan). The Thursday sessions (Jan. 17) began with a discussion of pathologic aspects (Harry Fang and Raymond D. Adams); methods for estimating cerebral blood flow (Gustav Nylin and Seymour S. Kety); experimental cerebral vascular disease (Joseph P. Whisnant); hypertension and cerebral vascular disease (A. C. Corcoran); and intermittent cerebral ischemia (Miller Fisher). The remainder of the program highlighted modern therapeutic approaches: dietary measures and the use of hormones directed to atherosclerosis (Jeremiah Stamler); report of 10 years' experience of anticoagulant therapy in cerebral thrombosis and embolism (Ellen McDevitt); experimental studies with enzymes (Eugene Clifton); the use of hypothermia in the surgical treatment of aneurysms (E. H. Botterell); and the evaluation of rehabilitation programs (Philip Lee). Among the distinguished discussers in the program were David Barr, Sir Russell Brain (London), P. C. Bucy, H. S. Dunning, W. T. Foley, R. W. Gerard, E. S. Gurdjian, Louis Hausman, H. Houston Merritt, Alfred Pope, Howard Rusk, Peritz Scheinberg, A. E. Walker, and Harold G. Wolff.... The first conference on cerebral vascular disease also was held in Princeton under the same sponsorship on January 24-26, 1954 (January 1954 Newsletter).

Briefs The spring 1957 meeting of the Research Advisory Board (Seymour S. Kety, chairman) of United Cerebral Palsy will take place in Detroit following the international symposium on the reticular formation, sponsored by the Henry Ford Hospital (Newsletter, February 1957).... J. G. Greenfield (London), distinguished neuropathologist, started another visit at the National Institute of Neurological Diseases and Blindness on February 23 for a period of six months.

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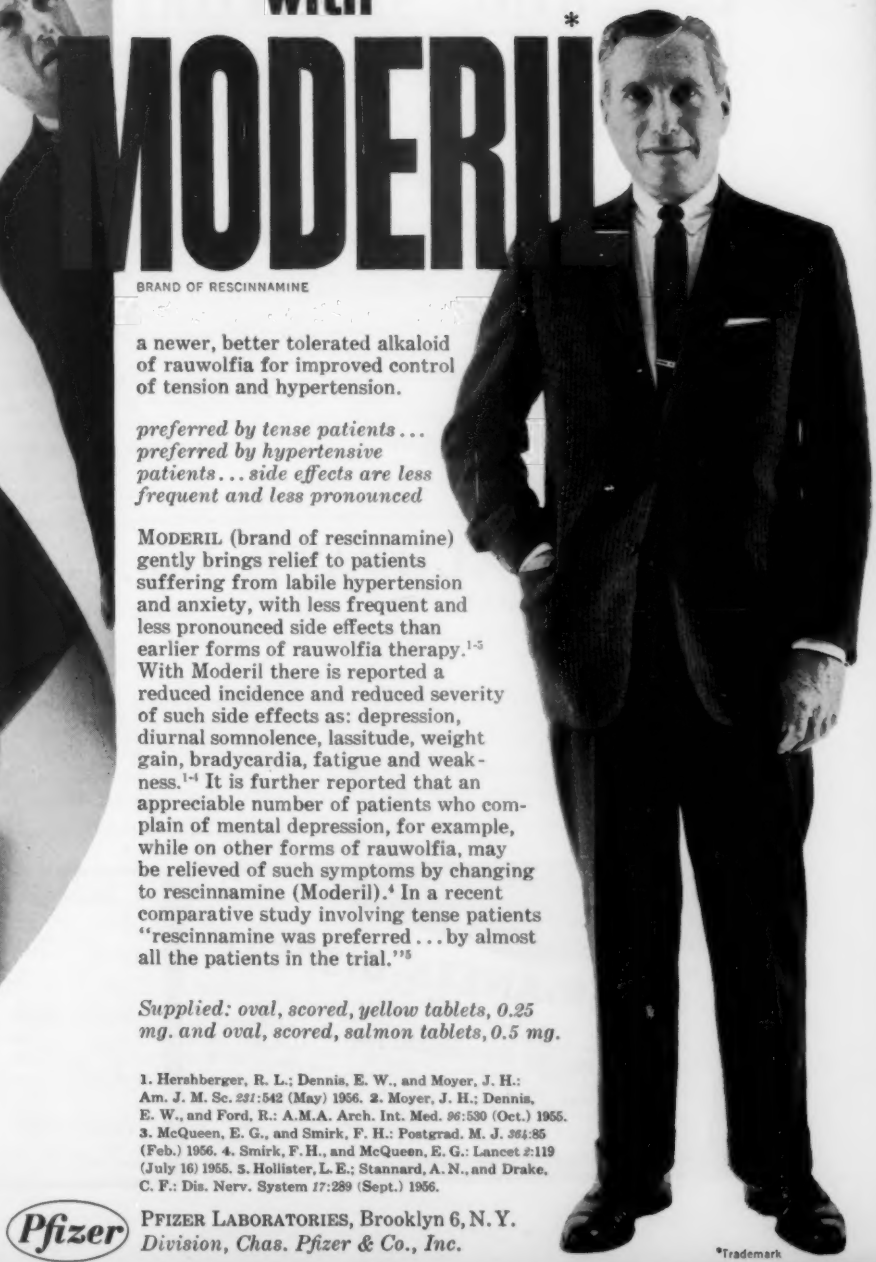

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July 20-21, Venice — SYMPOSIUM ON MEDICAL-SOCIAL ASPECTS OF SENILE NERVOUS DISEASES
July 28-Aug. 3, Brussels — XV^{e} INTERNATIONAL CONGRESS OF PSYCHOLOGY